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Session & Talks

Session I

Homeostatic regulation of medullary pain-related projection neurons in acute but not chronic pain

Ben Title

Pain hypersensitivity is associated with increased activity of peripheral and central neurons along the pain neuroaxis. On the other hand, in other neuronal systems, increased activity leads to adaptive reduction of neuronal excitability to maintain homeostasis. We show that at the peak of acute inflammatory pain, superficial medullary dorsal horn projection neurons (PNs) that relay nociceptive information to the parabrachial nucleus reduce their intrinsic excitability and, consequently, action potential firing. When pain resolves, the excitability of these neurons returns to baseline. Using electrophysiological and computational approaches, we found that an increase in potassium A-current (I_A) underlies the decrease in the excitability of medullary dorsal horn PNs in acute pain conditions. In chronic pain conditions, no changes of I_A were observed, and medullary dorsal horn PNs exhibit increased intrinsic excitability and firing. Our results reveal a homeostatic mechanism in acute pain conditions for regulating the output from the dorsal horn network, which, if lacking, could facilitate pain chronification.

Advisors: Prof. Alex Binshtok and Prof. Yosi Yarom

What makes human cortical pyramidal neurons functionally complex

Ido Aizenbud

Humans exhibit unique cognitive abilities within the animal kingdom, but the neural mechanisms driving these advanced capabilities remain poorly understood. Human cortical neurons differ from those of other species, such as rodents, in both their morphological and physiological characteristics. Could the distinct properties of human cortical neurons help explain the superior cognitive capabilities of humans? Understanding this relationship requires a metric to quantify how neuronal properties contribute to the functional complexity of single neurons, yet no such standardized measure currently exists. Here, we propose the Functional Complexity Index (FCI), a generalized, deep learning-based framework to assess the input-output complexity of neurons. By comparing the FCI of cortical pyramidal neurons from different layers in rats and humans, we identified key morpho-electrical factors that underlie functional complexity. Human cortical pyramidal neurons were found to be significantly more functionally complex than their rat counterparts, primarily due to differences in dendritic membrane area and branching pattern, as well as density and nonlinearity of NMDA-mediated synaptic receptors. These findings reveal the structural-biophysical basis for the enhanced functional properties of human neurons.

Advisor: Prof. Idan Segev & Prof. Mickey London

Unveiling the Developmental Pathway of Type 1 Dorsal Interneurons Through Single-Cell Transcriptomic Analysis and the Role of Retinoic Acid Signaling

Dina Rekler, Sarah Kagan, Noa Krutous, Gilgi Friedlander and Chaya Kalcheim

Understanding how the nervous system develops is essential for unraveling its complexity. The dI1 interneurons, located in the dorsal spinal cord and critical for proprioceptive function, provide an excellent model for studying neuronal development. We analyzed a single-cell RNA sequencing dataset from E4 quail embryos, capturing a snapshot of cells spanning from early progenitors to fully differentiated neurons, and offering insights into the dynamic processes and key molecular players shaping dI1 neuron development.

Through trajectory inference, we identified genes with significant expression changes during differentiation, revealing both established and novel functional pathways involved in dI1 maturation, such as synaptogenesis, neuronal signaling, apoptosis, etc. Using CRISPR-Cas9 knockdown, we currently investigate the functions played by selected genes belonging to the above pathways.

To further dissect these processes, we are testing the effects of selective inhibition of retinoic acid activity in developing dI1 interneurons, building on recent findings by Rekler et al., (2024) which demonstrated the critical role of retinoic acid in dorsal neural tube patterning. By integrating sequencing data with perturbation experiments, we aim to reveal specific functions of retinoic acid in dI1 development, distinct from its established roles in neural crest and roof plate development.

This study illuminates the regulatory networks governing dI1 interneuron development and has broader implications for understanding neuronal differentiation, as many of the identified mechanisms are shared across multiple neuronal subtypes. Our findings demonstrate the power of single-cell approaches in dissecting the complex molecular programs driving neuronal development.

Advisor: Prof. Chaya Kalcheim

Session II

How the Brain Handles Nonspecific Predictions: Evidence from EEG Responses to Visual-Auditory Pairs

Noa Guttman

The brain's ability to use previous knowledge to anticipate inputs has been extensively studied. In everyday life, cues rarely predict a single outcome. Yet, most existing research primarily measures prediction errors in scenarios with singular expected inputs. This leaves a gap in understanding how the brain predicts inputs when there are multiple potential outcomes. Does it rely on a condensed summary of possibilities for prediction, or does it hold discrete potential options?

We designed experiments pairing visual cues with auditory stimuli to address this question. In one condition, the cue did not predict the tone identity (no prediction condition); in another, it signaled a single expected tone (single prediction condition); and in a third condition, it signaled three equally probable tones (multiple prediction condition).

Previous studies show that event-related responses to predicted tones should be different from unpredicted tones. We hypothesized that if the brain produces a summary prediction in the multiple prediction condition, the response to the predicted tones should vary depending on their similarity to the single prediction. Conversely, if the brain maintains all the predictions, all responses should be similarly affected.

By applying cluster permutation analysis to EEG data recorded from 64 participants, we identified spatiotemporal clusters with significant differences between the tones under the multiple prediction condition. Interestingly, we found that the tone exhibiting a distinct response was the most informative tone for the task, and the cluster's activity in response to this tone resembled the activity observed in response to a specific prediction.

Advisor: Leon Deouell

A cellular model for live imaging of α -Synuclein aggregation in Multiple System Atrophy (MSA)

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α -Synucleinopathies, including Parkinson's disease (PD), multiple system atrophy (MSA), and dementia with Lewy body (DLB), are neurodegenerative disorders characterized by the accumulation of altered and aggregated α -Synuclein (α Syn) in the brain. α Syn is a 14.4kD protein, disordered in its physiological state, that tends to aggregate in a prion-like manner into different pathological states. These pathological states are the root cause of cell dysfunction and eventual death in those diseases.

MSA is a rare form of α -Synucleinopathy, unique for its cytoplasmic inclusions of α Syn in oligodendrocytic glial cells rather than neurons. The pathophysiology underlying MSA is poorly understood. Intriguingly, oligodendrocyte naturally express very little to no α Syn. In MSA, however, they either start to express α Syn or, absorb it from neighboring neurons.

In my research, I aim to study MSA pathophysiological cascade and the mechanisms underlying α Syn toxicity by generating an *in-vitro* system for imaging α Syn oligomerization. To mimic MSA, I used U373, a glia cell line that expresses oligodendrocyte markers, and was introduced with modified α Syn. In order to image α Syn only once it self-associates into its aggregated states, I utilized two techniques:

FRET-FLIM (Förster Resonance Energy Transfer - Fluorescent Lifetime Imaging Microscopy): Each α Syn molecule is labeled with a fluorescent marker (GFP and mCherry). Upon binding, the two fluorescent molecules are in proximity, allowing FRET to occur, quantified by changes in fluorescence lifetime.

BiFC (Bimolecular Fluorescence Complementation): Each α Syn molecule is labeled with half of Venus. Upon binding of two different α Syn molecules, Venus becomes whole and fluorescent.

Both systems will be used as valuable tools in the research of α Syn mechanism of polymerization, aggregation and accumulation as well as the cellular mechanisms employed to counteract these processes.

Blitz Lectures

What Determines Synaptic Weight in the Cortex?

Evidence from Connectomics

Dean Geckt and Toviah Moldwin

The Allen Institute Machine Intelligence from Cortical Networks (MICrONS) is an ambitious program to map the function and connectivity of cortical circuits, using high throughput electron-microscope (EM) imaging technologies combined with Ca-imaging. The dataset represents an unprecedented scale of neural circuit mapping, encompassing over 300 million synapses and 70,000 neurons, providing an unparalleled opportunity to investigate synaptic organization and connectivity patterns. Its goal is to provide insights into the computational principles that underlie cortical function. We used this dataset, spanning multiple visual areas in the mouse cortex, to investigate the distribution of the size of the synaptic cleft (of both inhibitory and excitatory synapses), which we use as a proxy for synaptic weight reflecting the information storage in the cortex. We analyze a variety of variables, spanning from the high-level anatomy to the micro-organization of synapses on the dendritic tree. This includes exploration of the relationship between cleft size and cell type, in-degree (input synapses) and out-degree (output synapses) distribution, examine excitatory-inhibitory balance per neuron, correlation between synaptic weight and synaptic distance from the soma, as well as various additional features that can be extracted from the MiCrONS dataset. Our analysis provides novel insight into how information is stored in the mouse visual cortex and, in particular, into the extent to which synaptic weights are a consequence of innate constraints versus the product of activity-dependent plasticity.

Advisor: Prof. Idan Segev

Simultaneous calcium and voltage Imaging in excitatory and inhibitory neurons in the mouse hippocampus

Michal Rubin, Shulamit Baror-Sebban, Yoav Adam

Two-photon Calcium imaging is a popular technique to study neuronal activity in behaving animals. While somatic calcium dynamics are considered a good proxy for spiking activity, there is mixed evidence supporting this assumption. We developed a bicistronic viral construct for co-expression of the voltage indicator Archon1 and the calcium indicator GCaMP8m. We also developed an imaging system allowing simultaneous high-speed voltage imaging and 2-photon calcium imaging. Using this toolkit we systematically compared the calcium dynamics to the ground-truth voltage signals of pyramidal cells (PCs) and interneurons (INs) in the mouse CA1. Our data revealed that calcium transients in PCs are linearly related to the firing rate (FR) in cases of regular spiking, but diverge from linearity during complex spike events. INs show high firing rates which often resulted in no apparent calcium activity. Carefully examining the voltage-to-calcium transformation in INs occasionally showed a positive correlation of the calcium with the FR while other cells displayed no correlation or slightly negative. Overall, our data call for careful interpretation of calcium imaging data, particularly in the case of INs. Furthermore, calcium is a key signal for learning and plasticity. The experimental approach we developed will allow detailed mechanistic studies of calcium-voltage dynamics during learning.

Advisor: Prof. Yoav Adam

Unveiling Mechanisms of Cognitive Resilience in Aging: Distinct Glial States in Super-Agers' Brains

Itamar Shahr, Roi Meir, Shmuel Cohen, Itai Weiss, Roi Segel, Ahmed Mohamed Disouky Mostafa, Orly Lazarov, Naomi Habib

The decline of cognitive abilities, such as processing speed and memory capacities, is one of the hallmarks of aging both in natural aging and all the more in pathological cases such as Alzheimer's disease (AD). Although cognitive decline is common with advanced age, some individuals demonstrate resilience, maintaining their cognitive abilities in aging, suggesting the presence of natural protective mechanisms that support cognitive resilience during aging.

In this study, we tested if "super-agers" that exhibit cognitive performance comparable to those 20 years younger, have a unique cellular environment that might provide protection. For this end, we profiled and analyzed cellular diversity by single-nucleus RNA sequencing (snRNA-seq) of hippocampal dentate-gyrus samples from 18 postmortem individuals, comparing super-agers to young, healthy aging, mild cognitive impairment (MCI) and Alzheimer's disease (AD). Our analysis revealed coordinated change in glial cells, identifying distinct glial states in the brains of super-agers not found in natural agers. We found that super-agers exhibited a cellular environment distinct from the one found in young brains, and diverging also from AD and MCI. We identified these protective glial states also in the prefrontal cortex and validated their association to resilience in a larger cohort of 437 aging brains.

For example, in microglia cells, we found three key microglial states: a disease-associated state, in individuals with AD and MCI; a homeostatic microglial state, predominant in young individuals; and a suggested protective microglial state, almost exclusively expressed in super-agers. The protective program was surprisingly associated with immune regulation and inflammation, and distinguished super-agers from healthy agers and young brains.

These findings highlight unique molecular adaptations in glial cells that may contribute to cognitive resilience in super-agers, offering novel insights into mechanisms of healthy brain aging and identifying potential therapeutic targets for mitigating neurodegenerative diseases.

Advisor: Dr. Naomi Habib

Pareto optimality reveals the computational goals of the human brain

Dan Hilman Amir

The human brain performs a wide range of computations to support complex behaviors, reflected in diverse activity and connectivity patterns. Among the myriad of complex functional connectomes, can one disentangle these into meaningful core computations? Here, we propose a principled framework for connecting the brain's functional organization to computations — Pareto optimality. Pareto optimality theorem posits that systems optimizing performance under multiple competing goals achieve this by balancing trade-offs within a low-dimensional space called the Pareto front. The Pareto front is spanned by archetypes that optimize each goal individually. Thus, Pareto optimality implies strong constraints on the architecture of systems performing under competing goals. We applied Pareto analysis to reveal the driving computations of the human brain's resting-state functional connectome (HCP dataset, N=1200). We found that resting-state functional connectomes lie on a low-dimensional triangle, consistent with the geometric constraints of the Pareto front. The three archetypes correspond to three core computational goals: 1) energetic efficiency 2) control and goal-directed processing 3) internal processing and memory. These goals are reflected in the archetypes' connectivity patterns, network topology and information flow measures, and behavioral and clinical associations. These core computational goals extend beyond resting-state, as the Pareto front provided an effective coordinate system for evaluating brain functionality. Dynamics on the Pareto front corresponded to task demands, correlated with task performance, and outperformed PCA dimensions in task prediction accuracy. Using two additional datasets (ADHD-200 and ADNI), we found differing characteristics of young adulthood and aging along the Pareto trade-off axes. On top of these dynamics, ADHD adolescents and Alzheimer's disease patients showed distinct locations compared to their age-matched neurotypical population. Finally, a minimalistic neural computation model demonstrated the fundamental nature of these computational trade-offs in information processing systems. Taken together, Pareto analysis indicated that the functional organization of the human brain at resting-state is shaped by trade-offs between three core computational goals. On a broader scale, Pareto optimality offers a novel, principled framework to link neural architectures to core computations across modalities, tasks, lifespan stages, clinical conditions, and populations.

Advisor: Dr. Yuval Hart

Involvement of amygdala neurons in male predominance of autism spectrum disorder

Noa Montefiore

Male predominance is one of the least understood characteristics of Autism Spectrum Disorder (ASD). While more than a hundred genes are involved in ASD, only a few of them show sex differences in behavior. In previous work, we found that male mice harboring a mutation in the *Pogz* gene (*Pogz*^{+/-}) show sexually dimorphic overly friendly behavior in several sociability assays. Mapping the engaged neurons during social recognition revealed that in *Pogz*^{+/-} males, there are more activated neurons in the basolateral amygdala (BLA) than in control and *Pogz*^{+/-} female mice.

To characterize the morphophysiological properties of those BLA neurons, we conducted in-vitro whole-cell recordings in acute brain slices from both *Pogz*^{+/-} and control mice. We employ targeted recombination in active populations (Trap2) to label the neurons in response to a social odor test. Preliminary results from single cell recording of BLA neurons present different types of principal neurons, characterized by unique AHP and spike train accommodation in response to a long current injection. Initial results also indicate that the neurons active during the social odor test exhibit characteristics similar to a specific subtype of the principal neurons we identified in the BLA. Further results are needed, and experiments are underway to collect more data.

This research will further expose any correlation between male predominance and overly friendly behavior and the basis of this neuronal network properties. Our results will pave the way to understand the role of amygdala neurons in ASD model mice and advance our knowledge about autism spectrum disorder.

Advisors: Yosef Yarom & Sagiv Shifman

The interplay between ApoE4 and Sex in Effecting Cellular Drivers of Alzheimer's Disease Progression

Yifat Haddad, Yuval Rom

Alzheimer's disease (AD) is a complex neurodegenerative disorder influenced by genetic and environmental factors, including ApoE4 and sex. This study investigates the interplay between ApoE4 genotype and sex in driving cellular changes associated with AD progression. We developed DeepDynamics, a novel deep learning method that leverages bulk RNA sequencing data to predict individual positions along AD and alternative brain aging trajectories. By analyzing 1,092 individuals from the ROSMAP cohort, we uncovered distinct pathological dynamics influenced by ApoE4 and sex. Our findings reveal that ApoE4 carriers exhibit accelerated amyloidopathy, tauopathy, and cognitive decline compared to non-carriers. Females show higher tauopathy and faster cognitive decline than males, with female ApoE4 carriers demonstrating the highest risk for AD pathologies. Causality analysis of the DeepDynamics model identified key cellular drivers of AD progression, including astrocyte subpopulation 10 (Ast.10) and oligodendrocyte subpopulation 7 (Oli.7), which are strongly associated with the ApoE4 allele.

Methodology and Results

We utilized single-nucleus RNA sequencing data from 437 aging brains to develop a comprehensive cellular atlas, characterizing 96 cell states across various stages of AD. This atlas formed the basis for defining two distinct aging trajectories: progressive Alzheimer's disease (prAD) and alternative brain aging (ABA). To enhance statistical power, we developed DeepDynamics, an artificial neural network trained on shared individuals' brains to predict aging trajectories for 1,092 individuals profiled by bulk RNA sequencing. This approach allowed us to exploit a larger dataset and investigate genetic risk factors as natural perturbation experiments

Key Findings

ApoE4 and Sex Effects: ApoE4 carriers showed significantly higher amyloidopathy, tauopathy, and cognitive decline rates. Females exhibited higher tauopathy and faster cognitive decline, with female ApoE4 carriers at the highest risk.

Cellular Drivers: The DeepDynamics model identified Ast.10 and Oli.7 as potential key drivers of AD progression, with Oli.7 showing a strong association with the ApoE4 allele.

Alternative Aging Trajectory: Astrocyte subpopulation 5 (Ast.5) and oligodendrocyte progenitor cell subpopulation 3 (OPC.3) were identified as influential in the alternative aging trajectory.

This study provides novel insights into the cellular mechanisms underlying AD progression and highlights the importance of considering both genetic risk factors and sex in understanding disease pathogenesis. Our findings may inform future targeted therapeutic strategies and contribute to a more comprehensive understanding of Alzheimer's disease.

Advisor: Dr. Naomi Habib

Session III

Brain-wide neural underpinnings of social behavior in zebrafish

Imri Lifshitz

To survive and reproduce, animals rely on social interactions with their conspecifics. The prominence of these interactions varies between individuals and develops over time. However, little is known about the precise underlying neural mechanism that drives a social action toward a conspecific. To address this question, we developed a novel experimental assay that records whole-brain neural activity in a focal fish while it observes and responds to a freely swimming conspecific. We show that focal fish tended to elicit a movement after a typical delay from a movement of conspecifics (synchronized movements). These synchronized movements were more likely to result in an approach toward the observed conspecific. To uncover the neural basis for this approach behavior, we tracked neural information from basic sensory features of the conspecific until the selection of an approach movement by the focal fish. Our results reveal a precise midbrain encoding of conspecific position and direction, alongside a brain-wide distinction between approach and non-approach movements. Specifically, we identified a neural signature emerging 5-10 seconds before the initiation of an approach movement, marked by reduced midbrain activity and elevated forebrain activity. These findings provide a detailed neural framework that connects sensory observation of a conspecific to the execution of social action, offering key insights into the neural basis of socially coordinated behaviors.

Advisor: Dr. Lilach Avitan

Coding time in cortical dendritic spines: An EM-based computational study

Sapir Shapira, Netanel Ofer, Idan Segev

Cortical pyramidal cells (PCs) are covered with thousands of dendritic spines—tiny protrusions with bulbous heads and thin necks—that serve as the main site for excitatory synapses where key plasticity and cortical computations take place. Recent dense electron-microscopic (EM) reconstructions of thousands of PCs from both mice and humans provide an unprecedented nano-scale view of the morphology and spatial distribution of dendritic spines. Leveraging these datasets with a newly developed EM-to-NEURON pipeline, we present the first compartmental models of complete PCs, including their spines. Notably, spine density varies significantly among different dendritic branches of the same neuron. Analysis of $\sim 200,000$ spines from 100 mouse and 100 human PCs reveals widespread variations of spine-neck diameter in individual spines; we show analytically that this results in a larger-than-expected spine-neck resistance (R_{neck}) that confers an ultra-fast membrane equalization time constant enabling spines to track rapid fluctuations of excitatory synaptic potentials (EPSPs) and effectively recruit fast-activated nonlinear ion channels embedded in the spine head membrane. At the dendritic branch level, spine-to-spine EPSP propagation velocities are estimated to range between 0.1 and 0.16 m/sec; decreasing with increasing spine density. Across the full dendritic arbor, we observe a distance-dependent broadening of the spine-head integration time window. These findings position dendritic spines as finely tuned timing devices, critical for synaptic computation and plasticity in cortical circuits.

Advisor: Prof. Idan Segev

Session IV

Binding of place and value in the Orbitofrontal Cortex

Abhishek Jangid

Choosing an appropriate goal location among multiple available options is crucial for survival and typically involves evaluating a location and its associated value. This task is further complicated when the value of the location changes with time. To ensure informed decision-making and efficient action planning, the brain needs to flexibly assign values to locations while maintaining an underlying spatial map that generalizes across different values. However, the neural basis of such flexible place-value binding remains poorly understood. Previous studies have shown that the orbitofrontal Cortex (OFC) represents goal locations during navigation, and encodes the economic value of options during decision-making. However, whether and how the OFC neurons encode both spatial locations and their associated values remains unknown.

In the current study, we implemented a goal-directed navigation task comprising multiple reward locations each dispensing varying reward amounts. In each trial, rats needed to navigate to a specific reward location. Importantly, the reward amount available at a given location varied throughout the session, necessitating flexible value updates. Analysing the error patterns revealed that animals tended to erroneously visit previously rewarded high-value locations compared to lower-value locations, indicating an association of place and value during task performance. Next, to understand the neural basis of place-value binding, we performed high-density neural recording from the OFC during task performance. As animals approached and licked a reward location, OFC neurons encoded both the location and its expected value, with a fraction of the neurons exhibiting conjunctive coding of both. At an ensemble level, OFC neurons preserved the spatial topology of the environment, such that the neural representational distance between a pair of reward locations was proportional to their physical distance. Different values of a location resulted in moderate shifts in their representations within the spatial map, thereby enabling decoding of the location value while preserving the overall spatial mapping. Importantly, a decoder trained on reward locations for a specific value could successfully generalize to other values, suggesting that the OFC spatial map can enable consistent navigational strategies across reward values. Overall, our results indicate that OFC is a key brain region that forms a topology-preserved map of salient locations while flexibly assigning values to these locations, resulting in a conjunctive place-value map that can facilitate informed and efficient spatial decisions.

Advisor: Dr. Raunak Basu

Longer lasting adaptation may underlie autistics' reduced cognitive flexibility

Vishnu Priya Sampath, Nathaniel Zuk, Ameer Alayan, Jaroslav Slobodskoy-Plusnin, and Merav Ahissar

Objectives

Accumulative studies suggest that autistics behavior is less flexible and which yields difficulties in dynamic environments. While there are several accounts for this observations, we tested a simple hypothesis: autistics' adaptation processes last longer. If such is the case – they will retain sensitivity to initially presented pattern and regularities as they will retain their pattern of adaptation for longer periods.

Methods

Participants performed a two-tone pitch discrimination task. They performed three blocks of 60 trials each. The inter-stimulus interval (ISI) was fixed at 750ms for all trials, whereas the inter-trial-interval (ITI) differed between blocks (4s, 8s, and 16s). The experiment began with 16s ITI and was followed, by blocks of 4s and 8s whose order was randomized. Behavioral performance and EEG data were recorded in neurotypical (NT) adults ($n=20$), and people with ASD ($n=20$) matched for age and cognitive abilities. Both ERP (focusing on N1 component produced by the auditory cortex) and behavior were measured.

Results

NT and ASD groups performed similarly overall (~80% correct). EEG data revealed that individuals with ASD do have longer-lasting adaptation. This was manifested in 2 ways: First, with 16 s ITI – N1 in autism was gradually adapted. This was not the case in NT, in line with reported literature that single stimuli with intervals >15 seconds do not yield long lasting adaptation. Second, the N1 produced by ASD with 8s ITI was as small as that produced by 4 s, mainly due to the long-lasting adaptation with 16s intervals.

Conclusions

ASDs' pattern of N1 adaptation suggests that it is indeed longer-lasting than NT, as it lasts long than 16s. This adaptation-elongation may interfere with the ability to tune and adapt to different patterns in volatile environments.

Keywords: Neural Dynamics, Adaptation, Autism, Accuracy Bias, EEG

Advisor: Prof. Merav Ahissar

Neural correlates of rapid learning in the Orbitofrontal cortex

Mousa Karayanni

Few-shot, rapid learning, enables us to swiftly grasp new knowledge and skills with little guidance or reinforcement. Computational studies emphasize the importance of abstract representations and generalization to rapid learning. Previous studies have revealed both correlative and causal relationships between the Orbitofrontal cortex (OFC) and these essential features of rapid learning. To directly investigate OFC with rapid learning, we developed a multi-step behavioral task to assess learning strategies in freely-moving rats while recording neural activity using untethered Neuropixels probes. Rats exhibited 4 or more episodes of rapid learning within single sessions, with near-optimal performance after only 1-2 rewards. The rats employed hierarchical, model-based problem-solving strategies, leveraging their understanding of task structure to achieve rapid learning. Electrophysiological recordings from the OFC revealed heterogeneous yet robust responses around task-related events, generating predictive and decodable task-related representations. Importantly, rapid learning was accompanied by systematic changes in neural responses, which reflected shifts in OFC information content.

Advisors: Prof. Eli Nelken & Prof. Yonatan Loewenstein

Early Neuronal Reprogramming is Shaping the Alzheimer's Disease Cascade

Roi Meir, Gali Schwartz, Naomi Habib

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction and neuronal loss that lead to cognitive decline and dementia. Recent large-scale efforts to map the cascade of cellular events leading to AD in human brains, revealed a coordinated response of all glial cells, emerging at early disease stages, and predicted to drive the progression of the disease. Yet despite the known damage to neurons in AD, these efforts did not uncover at which stage of the disease the alteration in neuronal cells occurs and to what extent are these driving the cascade of events leading to dementia.

Here, we applied a continuous modeling approach to capture cellular diversity in a large dataset of 1.7 million single nuclei RNA profiles from 437 aging and AD prefrontal cortex human samples. Instead of a traditional discrete classification approach based on clustering, we used Topic Modeling to model the continuous diversity of expression programs within each brain cell type. Using non-negative matrix factorization (NMF), the RNA profile of each cell is decomposed into multiple gene expression programs that together describe the activity of the cell. Next, we identify programs dynamically regulated along the cascades of disease and aging.

In neuronal cells, we uncovered a coordinated change in the expression programs across all neuronal subtypes along the AD trajectory. Interestingly, these neuronal changes occurred at an early disease stage, well before the reported neuronal damage and cognitive decline, suggesting neuronal reprogramming as an early driver event in the DA cascade. In AD, neurons down-regulated the expression of basic functions, including synaptic genes, suggesting early synaptic modulation or damage. Surprisingly, our results suggest that neuronal fate in AD included two distinct programs, one leading to oxidative-stress and apoptosis cell death, while the other leading to re-entry into the cell-cycle. These dramatic rewriting of neuronal cells is tightly linked to the previously observed changes in glial cells, including an early response in microglia and astrocytes and a later cross-glial stress response and loss of myelin production in oligodendrocytes accompanying a major loss of synaptic proteins.

Advisor: Dr. Naomi Habib

Session V

Probing the Circuit Underlying-Cocaine-Induced Stereotypies with a Novel Behavior Analysis Platform

Itay Shalom

The striatum is a primary target of cocaine, with its subregions showing differential sensitivity depending on the dose and treatment regimen. The ventrolateral striatum (VLS), in particular, is highly responsive to high doses of cocaine and plays a critical role in the execution of orofacial motor actions. However, the mechanisms by which interactions among neuronal subpopulations in the VLS contribute to the emergence of stereotypic actions remain poorly understood. In this study, we investigated the progressive development of orofacial and upper-limb stereotypies following repeated cocaine exposure and the role of striatal direct- and indirect-pathway spiny projection neurons (dSPNs and iSPNs, respectively) in regulating these behaviors. To achieve this, we developed a novel computational neuroethology platform capable of automatically annotating actions performed by freely behaving mice with high fidelity. This platform allowed us to precisely characterize the narrowing of natural action repertoires following cocaine exposure, culminating in a commitment to orofacial stereotypies. Using optogenetic activation of dSPNs and iSPNs, we uncovered a "Go-Switch" mechanism in the VLS. Activation of dSPNs promoted orofacial actions, whereas activation of iSPNs facilitated switching to non-orofacial behaviors. Fiber photometry recordings of dSPN and iSPN activity revealed a cocaine-induced dip in iSPN activity synchronized with the onset of floor licking behavior. Furthermore, chemogenetic inhibition of iSPNs exaggerated cocaine-driven surface licking, characterized by longer and more persistent bouts. Together, these results suggest a possible mechanism by which high cocaine alters the VLS SPNs dynamics, leading to development of orofacial and upper-limb stereotypies and providing a target for therapeutic intervention.

Advisor: Prof. Ami Citri

Autism spectrum disorder variation as a computational trade-off via dynamic range of neuronal population responses

Oded Wertheimer

Individuals diagnosed with autism spectrum disorder (ASD) show neural and behavioral characteristics differing from the neurotypical population. This may stem from a computational principle that relates inference and computational dynamics to the dynamic range of neuronal population responses, reflecting the signal levels for which the system is responsive. In the present study, we showed that an increased dynamic range (IDR), indicating a gradual response of a neuronal population to changes in input, accounts for neural and behavioral variations in individuals diagnosed with ASD across diverse tasks. We validated the model with data from finger-tapping synchronization, orientation reproduction and global motion coherence tasks. We suggested that increased heterogeneity in the half-activation point of individual neurons may be the biological mechanism underlying the IDR in ASD. Taken together, this model provides a proof of concept for a new computational principle that may account for ASD and generates new testable and distinct predictions regarding its behavioral, neural and biological foundations

Advisor: Yuval Hart

Late development of innate olfactory circuitry

Taha E, Shapira S, Nahari R, Yudco O, Givon M, Segev I, and Mizrahi A

Innate olfactory behaviors, such as attraction to food odors and avoidance from predator scents, are traditionally considered hardwired and functional at birth. However, the functional ontogeny of such behaviors and their underlying neural circuitry remain completely unknown. We show that odor attraction and avoidance behaviors emerge only late in postnatal development. Juvenile mice exhibited weak and inconsistent responses to attractive and aversive odors, while adults displayed robust preferences. Anatomical analyses revealed that mitral cell (MC) projections to the cortical amygdala (a known critical node for innate odor preference) are immature in juveniles. Tracing studies further revealed distinct anatomical and physiological biases between MCs projecting to the cortical amygdala versus those projecting to the piriform cortex.

Using two-photon calcium imaging and computational decoding of mitral cell population activity, we showed that juvenile MC ensembles exhibit inferior precision and reliability of odor representations as compared to adults. Adult MCs projecting to the cortical amygdala displayed robust and sustained responses to aversive odor, underscoring their specialized role in innate odor processing. Remarkably, using wireless optogenetics to activate MC projections to the cortical amygdala in juveniles, we restored innate odor preferences to adult-like levels. These findings challenge the notion of innateness-at-birth by revealing a gradual maturation process of olfactory circuits, highlighting their critical role in activating innate behaviors.

Advisor: Prof. Adi Mizrahi

Cross-Pollination @ ELSC: Integrating Cognitive and Systems Neuroscience to Study Autism Spectrum Disorder

Aviel Sulem, Benne Praegel, Jaroslav Slobodskoy-Plusnin, Adi Mizrahi, and Merav Ahissar

An overarching goal in our ELSC community is to join forces across disciplines to tackle some of the most challenging problems in neuroscience. Achieving this goal is inherently difficult, as it involves overcoming a range of obstacles—from differences in experimental design approaches to semi-cultural disparities across fields.

In this project, the Mizrahi and Ahissar labs joined forces to bridge this interdisciplinary gap, aiming to uncover the neural basis of cognitive biases in Autism Spectrum Disorder (ASD). Specifically, we started by proposing a novel mechanism for the atypical use of context in ASD, gaining insights by integrating mouse and human studies. To this end, we assembled an interdisciplinary team that combines systems neuroscience and cognitive neuroscience, enabling us to approach the problem from multiple perspectives.

We explored ASD through the lens of perceptual learning and behavioral biases. Using the 16p11.2 deletion mouse model of ASD, a well-characterized preclinical model, we compared behavioral performance in an auditory discrimination task between ASD mice and matched controls. This comparison revealed that ASD mice are particularly sensitive to reward – and tend to press following Hit responses. Namely, they tend to repeat responses that led to reward. This discovery sparked the idea of a human counterpart phenomenon, leading us to assess behaviorally and with EEG sensitivity to reward in humans. Here too we found enhanced sensitivity compared to neurotypicals.

Taken together, our work suggests a shared pathway underlying a cognitive effect in ASD. This collaboration not only yielded new insights and hypotheses but also drove innovative research directions that will contribute to a deeper mechanistic understanding of ASD. Further, our partnership exemplifies how cross-pollination between disciplines can break traditional boundaries, generating meaningful discoveries that push the field forward.

Advisor: Prof. Adi Mizrahi, and Prof. Merav Ahissar

Posters

Abstract (1) - Maor Nativ

Maor Nativ

Stimulus selectivity is a fundamental property of neurons in sensory systems, with individual neurons showing preferential responses to specific stimuli, such as faces in the medial temporal lobe, including regions like the hippocampus and entorhinal cortex. While previous research has demonstrated that stimulus selectivity can emerge in randomly connected networks, the robustness of this selectivity under noisy conditions remains poorly understood, particularly in recurrent network architectures.

In this study, we investigated the emergence and stability of stimulus selectivity in recurrent spiking neural networks, with random connectivity when presented with noisy stimuli delivered as Poisson input patterns. Using a detailed spiking neural network model implemented in BRIAN neural network simulator, we quantitatively assessed both neuronal selectivity and population sparseness through rigorous statistical measures.

Our results demonstrate that random network architectures, despite showing apparent selectivity in single presentations, fail to maintain consistent selective responses across multiple presentations of noisy variants of the same stimulus. This finding suggests that the robust stimulus selectivity observed in biological neural circuits likely requires structured connectivity patterns shaped by learning, rather than emerging spontaneously from random architectures.

These findings provide important insights into the relationship between network architecture and functional properties in neural circuits, suggesting that learning mechanisms are necessary for the development of robust stimulus selectivity in the presence of sensory noise.

Glial response shape neuronal survival in *ex-vivo* adult human brain tissue

Miriam Adam, Inbar Shapira, Daniel Kitsberg, Ido Palldor, Tal Shahar,
Naomi Habib

One of the major challenges of studying the human brain in health and disease, is the lack of live models of the adult human brain. Human organotypic slice culture model, which is derived from brain tissue resected during surgery, was proposed as an *ex-vivo* 3D model that enables long-term culturing of brain slices for perturbation experiments. Yet, its ability to capture the physiological cellular responses to stimuli of different brain cell types was not established to date. Here, we established the organotypic brain culture system and applied high-resolution profiling of cells by single nucleus RNA-sequencing (snRNA-seq). We showed that the cultured brain slices maintain the cellular diversity of neuronal and glial cells and that the broad cellular morphology and the overall tissue structure is intact.

To establish the model we first showed that the brain cells in the cultured slices display the physiological response to external stimuli. Specifically, we investigated the response to TNF α , a pro-inflammatory cytokine, suggested as an early triggering event in aging and Alzheimer's Disease. We identified the canonical inflammatory response that was shared across glial cell types, as well as cell type-specific induced expression programs, identifying for example, induction of mitophagy related genes to be specific to astrocytes in response to TNF. By in-silico analysis of cellular interaction networks, we predicted an increase in unique cell-cell signaling following inflammatory stimuli, surprisingly identifying oligodendrocyte precursor cells (OPCs) as major signaling hubs especially to astrocytes.

Moreover, we longitudinally tracked the changes in neuronal and glial cells in culture by snRNA-seq, to record changes in human glial cells along a time line of neuronal injury and recovery. This analysis uncovered coordinated activation of microglia and astrocytes that were accompanied by changes in oligodendrocyte lineage cells. To better understand the effect of glial changes on neuronal health we compared two culturing conditions that differed in the extent of neuronal survival. We found that better neuronal survival was accompanied by increased rates of oligodendrocyte renewal. Furthermore, we uncovered distinct activation states in microglia and in astrocyte cells that were associated with culturing conditions that improved neuronal survival rates, which appeared early along the first days of culturing.

Overall, we showed that human brain organotypic slice cultures provide an exciting model to functionally interrogate molecular mechanisms in brain cells on a multicellular level. Our work highlighted the role of specific glial cell states in promoting the fate of neuronal cells and potentially promoting neuroprotection and repair.

The neural mechanism underlying fast and slow value-based decision processes

Adria Dym

During decision making, animals rely on fast, nearly automatic processes as well as slower, deliberative processes, which are likely supported by different neural mechanisms. Investigating these processes in parallel, in controlled behavioral tasks provides insight into the neural mechanisms underlying the components of decision-making.

We trained water-restricted mice on an auditory Go No-Go task incorporating an impulsivity component. Using behavioral analyses, we revealed two distinct licking patterns, each operating over different time scales, and modulated by the value of the learned stimuli: a fast all-or-none response triggered at the onset of stimuli, and a slower response with a ramping pattern.

To identify the neural circuits involved, we injected muscimol (or saline as control) into different brain areas prior to task execution. Our findings reveal that inactivating the lateral orbitofrontal cortex (lOFC) eliminated the slow component while preserving the fast component. In contrast, inhibition of the anterior lateral motor cortex (ALM)—a key region involved in sensory-cued licking—abolished both components. Similarly, inhibition of the ventrolateral striatum (VLS), a downstream target of ALM, produced the same effect as ALM inactivation. We are currently investigating the source of input responsible for the initial fast component.

Together, our work began to uncover the neural pathways underlying these two distinct behavioral processes, shedding light on the neural computations driving fast and slow components of decision-making.

Advisors: Prof. Adi Mizrahi, Dr. Eran Lottem

Development of the Spinal Cord Meninges in the Avian Embryo

Inessa Litvin, Susanna Ventriglia and Chaya Kalcheim

The development of the spinal cord and its surrounding meninges is a complex process, yet the origins and roles of the meningeal layers remain unresolved. While initially thought to arise from ectodermal tissues, the mesenchymal appearance of the meninges suggested a mesodermal origin. Traditionally viewed as protective, recent studies indicate a more active role for the meninges in central nervous system (CNS) development and function. Although previous research has demonstrated neural crest (NC) contributions to cerebral meninges, the origin of spinal cord meninges remains debated, with two primary candidates: the somites and the neural tube (NT)/NC cells. Studies in quail-chick chimeras suggest somite-derived cells contribute to meningeal structures at the trunk level, whereas NC and NT cells show limited involvement in this region.

To address this controversy, we first adopted a candidate approach to identify early markers of avian meninges that would serve for further functional studies. Second, we began investigating the embryological origin of trunk-level meninges. Using electroporation (EP) and lineage tracing techniques in quail embryos, we identified somite-derived cells that co-express meningeal markers, indicating their migration to the meninges. In contrast, EP of NT cells showed no contribution to meningeal structures. These findings support the hypothesis that somites contribute to specific meningeal layers and/or cell types, while NT-derived cells do not. Ongoing studies aim to further characterize the molecular and cellular composition of the spinal meninges and their developmental origins.

Advisor: Prof. Chaya Kalcheim

Mapping Brain Iron with Quantitative MRI: Validation and Applications

Maryana Pozin

Iron regulation in the brain, influenced by compounds such as ferritin, transferrin, and ferrous ions, is critical for normal brain function and is implicated in aging, neurodegenerative diseases. Recently, a quantitative MRI (qMRI) based approach was proposed to in vivo estimate the iron homeostasis (Filo et al 2023). In this method the dependency between two MRI relaxation $R1$ and $R2^*$ rate constants is estimated ($r1-r2^*$ relaxivity). In this work we validate this qMRI technology using an independent dataset of healthy young and old subjects and Parkinson's disease (PD) patients, by comparing it to known histological results (Connor et al 1992, Loeffler et al 1995).

qMRI scan from 87 subjects scanned in the Hebrew University (Drori et al BioRxiv). From each subject $R1$, $R2^*$ and the $r1-r2^*$ relaxivity were estimated in 11 brain regions of interest (ROI). In vivo brain values ($R1$, $R2^*$, $r1-r2^*$ relaxivity) were compared with ex vivo published quantification of iron compounds on the same ROIs.

Our analysis revealed consistent results, with in vivo qMRI scans correlating with ex vivo iron quantification. Specifically, $R2^*$ highest correlation was to iron content ($R\text{-sq}=0.76$ $p=8.1e-9$) and $r1-r2^*$ highest correlation was with iron mobilization ($R\text{-sq}=0.68$ $p=1.6e-7$). This reinforces the reliability of this qMRI-based method for assessing brain both iron fraction and iron homeostasis. A detailed analysis using ANOVA and Tukey's post-hoc tests to compare groups within the regions of ex vivo and in vivo values revealed inconsistencies in group differentiation between iron levels and $R2^*$ in the Globus Pallidus and Putamen, as well as between $r1-r2^*$ and iron mobilization in the Globus Pallidus and Caudate. These discrepancies may be attributed to the limited number of subjects.

This non-invasive qMRI method offers a valuable tool for monitoring brain iron homeostasis and could enhance the diagnosis and understanding of disorders related to impaired iron regulation. Establishing the relationship between in vivo and ex vivo iron regulation opens the way for future research relating specific brain regions at disease states (e.g., PD) and the impact of specific genetic subgroups.

Advisor: Prof. Aviv Mezer

Investigation of pathway downstream of striatum reveals potential non-canonical role of SNr in behavioral initiation

Mohammad Tamimi

The substantia nigra pars reticulata (SNr) (along with the globus pallidus externus (GPe)) is central to the basal ganglia's role in motor behavior modulation, processing complex neural inputs to orchestrate motor control. In the traditional basal ganglia model the direct pathway inhibits the SNr to facilitate action selection. Recent findings challenge this straightforward dichotomy, suggesting more nuanced interactions within these pathways. Utilizing optogenetics and fiber photometry, our study traces calcium activity in SNr neurons receiving inputs from either the orofacial-associated ventrolateral-striatum (VLS) or the lower-limb-associated dorsolateral-striatum (DLS) as freely-moving mice perform orofacial behaviors. Surprisingly, we observed a significant increase in activity in VLS-associated SNr neurons that predominantly correlates with the initiation of orofacial behaviors. This result was surprising given the well-documented activity of canonically SNr-suppressing, direct pathway striatal-neurons coincident with behavior initiation. There was also an increase in activity in DLS-associated neurons, though slightly less pronounced and temporally aligned with the full-body component of orofacial behaviors, such as pre-lick posture-adjustment and body-turning before body licking. These results indicate that the SNr may require robust activity to selectively inhibit directly competing behaviors, rather than uniformly suppressing unrelated actions. We are now turning our attention to GPe neurons downstream VLS and DLS.

Advisor: Prof. Ami Citri

A Localized Bilateral Depletion Approach for Studying the Role of Dopamine in Normal and Pathological Behavior

Shira Planer

The striatum exhibits a regional organization with relation to behavioral control, such that the dorsomedial aspect of the striatum (DMS) is associated with control of locomotion, while the lateral aspect of the striatum exhibits a humuncular organization, with the dorsal segments controlling body posture (trunk), followed by lower limb, upper limb and mouth, proceeding ventrally.

Dopamine depletion from the striatum underlies Parkinson's disease, for which the predominant treatment is dopamine replacement therapy with levodopa, which often causes levodopa-induced dyskinesia (LID). We developed a model of bilateral dopamine depletion localized to the ventral aspect of the dorsal striatum (VLS), aimed at inducing orofacial stereotypies following exposure to levodopa (oLID), which we could quantify using a machine-learning behavioral annotation framework developed in-house (STEREO). We found that mice with VLS depletion exhibited increased pronounced grooming and body-licking behaviors following exposure to levodopa, and increased licking following cocaine administration, while dopamine depletion from the DMS caused reduced licking and increased locomotion, compared to both VLS-depleted and naive mice. Our findings illustrate the development and utility of a localized model of oLID. Future research will examine the roles of direct and indirect pathways in these behaviors, potentially illuminating mechanisms underlying orofacial dyskinesia and contributing to therapeutic strategies for related side effects.

Advisor: Prof. Ami Citri

Context Shapes Behavior and A1 Activity in Mice Performing an Auditory Change-Detection Task

Gabrielle Marmur, Haneen Rajabi, John Schwarcz, Robert Reiner, Eran Lottem

Efficient sensory decision-making requires integrating dynamic contextual information with local sensory inputs. Here, we use an auditory change-detection task in which mice need to adapt their behavior in a context-dependent manner. This task allows us to test whether mice adapt to global contextual cues or rely solely on local stimulus features, as identical auditory stimuli can appear in different contexts. Behavioral data indicate that mice successfully modify their licking behavior in response to the same stimulus based on global contextual cues, demonstrating flexible decision-making. Neural recordings from the primary auditory cortex (A1) of behaving mice revealed that responses to sound were also modulated by context. These findings demonstrate that both behavior and A1 activity are shaped by global contextual parameters, extending beyond the immediate sensory history. Our results highlight how contextual statistics influence sensory processing and decision-making, providing insights into the neural mechanisms underlying adaptive behavior in dynamic environments.

Advisor: Dr. Eran Lottem

Statistical awareness: Is there a correlation between success in a statistical learning task and the level of awareness of the subject to the statistical regularity of the task?

Einav Avraham

Statistical learning (SL) is typically assumed to be a core mechanism by which organisms discover regularities in the environment through implicit learning not requiring awareness of the regularity. We investigated participants' success in a statistical learning (SL) task and their level of awareness to the regularities in the input, to examine how such awareness correlates with performance. Sixty-one participants took part in a two-stage spatial SL experiment, and we tracked their predictive eye-movements toward predictable vs. unpredictable stimuli in a computerized game requiring subjects to click at one of 8 screen positions where a target appears. Predictive eye movements toward predictable stimuli indicated regularity learning. Following the experimental session, participants provided answers to a questionnaire, indicating their awareness of the regularity. Results from our initial experiment showed a significant and high Spearman correlation between subjects' reported awareness to the statistical regularity, and their actual success in the task, which contrast some existing findings and assumptions in the SL field. While these findings are intriguing, further investigation is needed to validate and understand the relation between awareness to regularity and task performance in SL experiments and its implications within the broader context of the research.

Advisors: Prof. Ram Frost, Prof. Leon Deouell

Dopamine prioritizes reward certainty over size, diverging from choice behavior

Yirat Henshke, Eran Lottem and Mati Joshua

Dopamine (DA) plays a critical role in processing reward, motivation, and motor control. Its significance is evident in conditions such as Parkinson's disease, depression, and addiction, which arise from dopamine depletion or imbalance. Despite its importance, real-time measurements of DA activity during behavior have posed significant challenges, particularly in primates. In this study, we utilized a novel dopamine imaging technique to measure DA levels with sub-second resolution in behaving monkeys, focusing on the striatum—a central hub for reward processing and decision-making.

While DA is known to encode reward probability and size, the interplay between these dimensions poses behavioral challenges that remain poorly understood at the neural level. To address this, we recorded DA activity using fiber photometry from the striatum of a monkey, in behavioral tasks combining varying reward sizes and probabilities.

Our findings reveal several key results. First, DA signals conformed to reward prediction error (RPE) theory: at cue presentation, DA levels increased in proportion to the predicted reward's size and probability. At reward delivery, DA responses were inversely related to outcome predictability, with larger deviations observed for unexpected outcomes. Second, both in the DA activity and the monkeys' behavioral preferences, we found many deviations from representation of the expected value. Third, when comparing behavioral preference to dopamine we found that although DA signals often aligned with target choices, they exhibited an overrepresentation for conditions with 100% reward probability. Notably, even when the monkeys preferred a non-certain alternative target, DA activity was larger for the 100% reward, revealing a divergence between DA signaling and behavior.

These results provide critical insights into DA's role in integrating reward dimensions and influencing behavior. This study's innovative approach to measuring dopamine in monkeys offers a powerful tool for exploring DA's role in complex behaviors and decision-making processes.

Advisor: Prof. Mati Joshua

Cerebellar modulation of Basal Ganglia activity during motor behavior

Asia Prag

The cerebellum and basal ganglia (BG) are key subcortical structures that play a key role in motor timing, coordination and adaptation through distinct yet interconnected subcortical-to-cortical loops. Recent findings highlighted structural and functional cross-links between these two systems, with a particular role of cerebellar output in modulating different aspects of BG activity. However, we know little about the functional contribution of this cerebellar-to-BG link in planning and executing voluntary movements.

To address this question we trained a macaque monkey (*Macaca Fascicularis*) to perform a center-out delayed reaching task by interacting with a touch screen. Single-unit and multiunit activity were recorded from the sensorimotor cortex and BG structures including the striatum (STR), globus pallidus externa (GPe), and globus pallidus interna (GPi) using multichannel linear probes. Chronic stimulating electrode was implanted in the superior cerebellar peduncle (SCP) to activate/block cerebellar outflow.

We found that cerebellar stimulation evoked short-latency STR responses whereas GP response was weaker and occurred at longer latencies. The STR response latency matched the latency of the cortical response to SCP stimulation consistent with a subcortical (trans-thalamic) cerebellar-to-striatum link. Next, we quantified the tendency of BG cells (n=299) to express task-related activity and found that 59.8% of STR cells, 67.6% of GPe cells and 60.4% of GPi neurons were task-related. Unlike the similar tendency for task-related activity across BG neurons, directional tuning was more frequent in the GP (35.3% of GPe, and 45.3% of GPi neurons) than striatal neurons (25.1%). Finally, we found that the population-based coordinated activity in the GP but not in the striatum was strongly modulated by task parameters (i.e., direction of movement). Blocking cerebellar output disrupted and compressed task-relevant neural trajectories in the GP, highlighting the role of cerebellar signals in shaping BG task representation.

Our findings verify the functional link between cerebellar output and the BG. The results further highlight the impact of cerebellar signals to the dynamic regulation of BG activity during motor planning and execution and suggest that these two systems work in synergy to facilitate adaptive motor control.

Advisor: Prof. Yifat Prut

Title: Direction-specific role of cerebellar signals in preparation and execution of reaching movements

Nirvik Sinha

The cerebellum is well-known for the online control of movement timing and coordination. However, it is still unclear whether the movement deficits observed in cerebellar disorders arise due to defects in motor preparation itself. To answer this question, we trained two monkeys to perform center-out delayed reaching movements on a vertical touchscreen. The cerebellar output was reversibly blocked by high-frequency (130 Hz) stimulation of the superior cerebellar peduncle using a chronically implanted electrode. Cerebellar block disrupted movement timing and quality, as evidenced by increased reaction times and reduced peak hand velocities. Neural recordings from the primary and premotor cortices revealed diminished movement-related activity, with greater reductions in neurons tuned to anti-gravity (higher) targets. Moreover, cerebellar block also reduced the ramping preparatory activity especially in the premotor cortex following the visual cue to movement. To further explore the effect of cerebellar signals on the pattern of activity across the cortical neurons, we examined the underlying neural manifolds. Cerebellar block increased the dimensionality of the neural manifolds during both motor preparation and execution. Furthermore, the pattern of activity during preparation under cerebellar block was strongly misaligned to the control condition. This disruption impaired the orderly transition of the neural activity from the preparatory to the execution subspace, with regression analyses showing reduced predictive power of preparatory activity on subsequent movement-related activity, particularly for higher targets. Taken together, our results establish that cerebellar signals are essential for linking preparatory neural activity to subsequent execution-related activity, ensuring accurate and timely movements. Beyond its known role in motor-coordination, the cerebellum thus facilitates the generation of cortical activity patterns that underlie motor planning and execution, particularly for challenging anti-gravity movements.

Advisor: Prof. Yifat Prut

Training Large Neural Networks With Low-Dimensional Error Feedback

Maher Hanut

Training deep neural networks typically relies on backpropagating high-dimensional error signals—a computationally intensive and biologically implausible process. However, since most tasks involve low-dimensional outputs, we propose that low-dimensional error signals may suffice for effective learning. To test this hypothesis, we introduce a novel local learning rule based on Feedback Alignment that leverages indirect, low-dimensional error feedback to train large networks. Our method decouples the backward pass from the forward pass, enabling precise control over error signal dimensionality while maintaining high-dimensional representations. We begin with a detailed theoretical derivation for linear networks, which forms the foundation of our learning framework, and extend our approach to nonlinear and convolutional architectures. Remarkably, we demonstrate that even minimal error dimensionality—on the order of the task dimensionality—can achieve performance matching that of traditional backpropagation. Our rule efficiently trains convolutional networks, previously resistant to Feedback Alignment, with minimal error. This breakthrough not only paves the way for more biologically plausible models of learning but also challenges the conventional reliance on high-dimensional gradient signals in neural network training. Our findings suggest that low-dimensional error signals can be as effective as high-dimensional ones, prompting a reevaluation of gradient-based learning in high-dimensional systems. Moreover, we show that the dimensionality of the error affects the emerging receptive fields, opening new avenues for studying neural representations.

Advisor: Prof. Jonathan Kadmon.

Coordinated gene expression in the brain-spinal cord-muscle uncovers early muscle reprogramming in Alzheimer's disease

Anael Cain, Hans-Ulrich Klein, Yuval Rom, Aron Buchman, Naomi Habib

Advanced age is associated with cognitive impairment as well as motor dysfunction, yet whether these two systemic aging-deficits are linked is largely unknown. Specifically, within muscle tissues, which are part of the motor system along with the brain and spinal cord, atrophy and molecular changes with aging are well documented. We examined whether age-associated changes in muscle tissue are coordinated with changes in the brain and spinal-cord and to what degree do these changes contribute to motor and cognitive decline?

For this end, we profiled three tissues of the motor system: muscle, spinal cord, and supplementary motor area (SMA) by bulk RNA sequencing from 450 aging individuals, covering a range of cognitive and motor abilities. Within each tissue, we model the diversity across individuals by defining co-expression gene programs, using Weighted Correlation Network Analysis (WGCNA). Across the three tissues, we uncovered shared patterns of programs coordinated between individuals. For example, we found coordinated expression of genes related to energy production and metabolic processes in a subset of individuals, and coordinated expression of inflammatory genes in a different subset of individuals, showing coordinated processes between muscle, spinal-cord and brain SMA region.

Next, we tested the connection between programs to motor and cognitive decline. Surprisingly, we discovered a strong association between muscle programs to the rate of cognitive decline (dementia) and to Alzheimer's disease (AD) pathologies, and to a lesser degree this trend was also found in the spinal-cord and the SMA. Further exploring this intriguing link, we leveraged an available high-resolution cellular atlas of the aging dorsolateral prefrontal cortex (DLPFC) from 500 individuals, which assigned individuals along cascades of Alzheimer's Disease (AD) and alternative brain aging. Using a new deep learning algorithm, we aligned the muscle programs along the cascades of AD and aging. We uncovered three types of muscle reprogramming with age: "healthy" programs that decrease in the muscle along both processes of aging and disease, "aging" programs that increase along both cascades, and "disease" programs that appear only along the cascade of AD. Interestingly, the disease programs appear early, before the severe damage to neuronal cells and the clinical diagnosis of dementia, suggesting muscle tissues are altered early in the cascade of events leading to Alzheimer's disease. These findings, transform our understanding of the interconnected roles of muscle and brain and their crosstalk in the processes of aging and Alzheimer's disease.

Advisor: Dr. Naomi Habib

Astrocytic activation induces cognitive enhancement and Ab plaques shrinkage in an Alzheimer's mouse model

Yaara Weinstein

Long-lasting memories define who we are and how we experience the world. Inability to form and access these memories, as in neurodegenerative conditions such as Alzheimer's disease (AD), degrade the quality of life and impose a major burden on healthcare systems and society. Unfortunately, medical treatments that can prevent, slowdown, or reverse memory deficits are almost non-existent. To develop new strategies for targeting diseases associated with memory impairments novel mechanisms must be effectively harnessed for therapeutic value.

Interestingly, several studies reported abnormalities in both the number and function of *astrocytes* in human AD patients and in animal models of this disease. Work from our lab and others has revealed the ability of astrocytes to communicate with, and affect, neurons in the brain. Specifically, we have found that in normal mice direct astrocytic activation using chemogenetic or optogenetic tools is sufficient to induce hippocampal long-term synaptic potentiation, and activation of astrocytes during learning improves memory allocation, resulting in enhanced recall.

To test whether astrocytes can increase cognitive function not just in normal mice but also in impaired memory in Alzheimer's model mice, we expressed the Gq-coupled designer receptor hM3Dq in astrocytes which allowed their time-restricted manipulation by the application of the designer drug clozapine-N-oxide (CNO), in the CA1 of 5XFAD mice. Chronic CNO administration for 2 weeks in the drinking water caused an improvement in memory in the radial arm water maze task (RAWM) and a decrease in amyloid beta (A β) plaques volume, that was accompanied by a decrease in microglia number and an increase in neuronal activation. The 5XFAD mice showed not just enhanced memory, but reached the same level as the controls, that have improved themselves. In addition, there is an increase in A β clearance after one day of astrocytic activation. Moreover, a single CNO injection increased LTP and neuronal activity in 5XFAD mice. Chronic astrocytic activation for a year resulted in a long improvement in memory in 5XFAD mice in the RAWM, and a decrease in A β plaques. Interestingly, mice that received CNO for 2 weeks showed memory improvement right after it, and also after 2 weeks without CNO. The improvement was not evident after 6 weeks without CNO.

In summary, astrocytic activation can rescue memory performance after it already deteriorated, and partially clear existing A β plaques, showing the therapeutic potential of astrocytes in AD.

Advisor: Prof. Inbal Goshen.

All-optical electrophysiology reveals behavior-dependent dynamics of excitation and inhibition in CA1

Qixin Yang

Neuronal integration in the hippocampus is dynamically modulated by behavior through changes in excitatory (E) and inhibitory (I) inputs, which shape spiking output and modulate response gain. Using simultaneous voltage imaging and optogenetic depolarization in genetically defined cell types, we characterized the input-output function of key excitatory and inhibitory cell types within CA1 of awake-behaving mice. Our results demonstrate firing rates in principle pyramidal cells (PCs) and vasoactive intestinal peptide (VIP)-expressing interneurons (INs) decreases during locomotion, while the activity of somatostatin (SST) and parvalbumin (PV)-expressing INs increases. Using prolonged optical depolarization, we revealed that subthreshold theta oscillations in both PV and SST INs are mostly driven by excitatory inputs, while in PCs and VIP cells, they are driven by inhibition. By measuring the firing rate in response to short optical stimulations at increasing intensity (F-I curves), we directly assessed how the behavioral state modulates neuronal gain. We found that each cell type displays a different mode of gain modulation, with PCs showing significant gain modulation during locomotion. Remarkably, this profile was specific to their bursting activity while simple spikes remained unaffected. A two-compartment model suggested that this result could be explained by a balanced increase in the E and I background inputs to both the somatic and dendritic compartments. Lastly, we used our dataset to develop a simple classifier that could identify the different cell types with high accuracy based on the depolarized spike waveforms. These data provide a comprehensive picture of the nuanced interplay among hippocampal neurons that contributes to state-dependent regulation of neuronal activity, E/I balance, and theta oscillations.

Advisor: Prof. Yoav Adam

Expectation and surprise in the sleeping brain: No Auditory omission prediction error response in NREM and REM sleep

Sharon Yakim

Sleep is a reversible condition of reduced awareness and responsiveness to the external environment. Nevertheless, even during sleep, organisms must regularly sample the environment, create predictions, and detect their violation. Indeed, compelling evidence indicates that the sleeping brain can detect simple sensory deviation. However, only a few studies investigated more complex predictions, and it remains unclear how sleep modulates the formation of predictions and surprise responses. To answer this question, we recorded high-density EEG from healthy participants in sleep and wakefulness while they passively heard an auditory oddball-omission paradigm. The paradigm included expected and unexpected omitted sounds with intermediate complexity rules, which enabled us to disentangle between the neural response to the "pure" prediction error and the neural response to the stimulus's physical properties. In wakefulness, ERP analysis showed a significantly increased negativity at 100-300ms in central electrodes following omission onset in the unexpected omission condition compared to the expected omission. However, this omission expectation sensitivity was not evident in sleep. These results imply that the sleeping brain's ability to create predictions more complex than a mere sensory deviation is compromised.

Advisor: Dr. Anat Arzi

When are individual elements of naturalistic events encoded?

Noga Gilad

While viewing film clips, increases in hippocampal activity at event boundaries have been associated with better gist memory for the preceding event. Accordingly, some have argued that event segmentation during perception creates the units of episodic memory, and that events are encoded by the hippocampus at boundaries. It remains unclear, however, whether finer-grained elements that comprise events are also separately encoded online, as they are encountered, in addition to the gist representation encoded at event offset. This is because previous studies have only tested gist memory for short, temporally uncontrolled events. Further, prior studies of event encoding did not distinguish between different levels of boundary. In real life longer “coarse-grained” events (e.g., dinner) subsume clusters of brief “fine-grained” events (e.g. cooking and consuming), which in turn may comprise several yet finer-grained elements, including actions (e.g., “chopping carrots”). In the context of an event hierarchy, it is unclear which level of boundary might trigger encoding. This in progress study uses fMRI to measure brain activity while participants view a custom-made animated video, which comprises semi-naturalistic events organised into a partonomic hierarchy, with each lowest-level event depicting a character completing discrete actions (e.g., playing chess, hovering). Following scanning, participants complete a cued recall test for the actions. We will determine whether elements (actions) of prolonged events are encoded by the hippocampus online, or at the boundaries at event offset. If encoding occurs at boundaries, we will additionally be able to determine the level of boundary that triggers encoding of event elements.

Advisor: Dr. Aya Ben-Yakov

Perturb-seq reveals divergent and convergent pathways in autism associated genes through early cortical differentiation

Elad Dvir

Autism Spectrum Disorder (ASD) is a group of symptomatically heterogeneous neurodevelopmental disorders. ASD is known to have a strong genetic basis; however, its genetic architecture is very complex. The heterogeneity of the symptoms may stem, at least partially, from genetic heterogeneity. In this study, we employ a combined approach of CRISPR screening and single-cell RNA sequencing (Perturb-seq) to examine the effects of mutations in 39 high confidence ASD-associated transcription regulators on early in-vitro cortical differentiation of human embryonic stem cells. Our findings reveal that mutants tend to exhibit premature differentiation towards either neuronal cells or oligodendrocyte (OD)-like cells, correlating with known human phenotypes of the same genes. For example, perturbations that increase OD-like cells are more likely to be associated with microcephaly, while perturbations that decrease OD-like cells and increase neuronal cells are more likely to be associated with macrocephaly. Additionally, integrating cell-type composition changes with gene expression data enhances the distinction between genes predominantly associated with ASD and those predominantly associated with developmental delay. Our results advance the understanding of the genotype-phenotype relationship in ASD, potentially aiding in the identification of genetic subgroups within ASD and the development of targeted treatments.

Advisors: Eran Meshorer and Sagiv Shifman

Towards life-long learning in rats

Nimrod Agassi, Mousa Karayanni, and Israel Nelken

While synaptic plasticity is believed to underlie learning and memory formation, theoretical work suggests that learning new memories may interfere with old ones, and the mechanisms underlying life-long learning remain largely unexplored. This study describes initial attempts to achieve life-long auditory learning in rats and reach its limits. Theoretical work suggests a limited capacity for memory formation and retention in neural networks, depending on network size. In most models, memory capacity is proportional to the size of the network. Considering that the rat auditory cortex is approximately 100 times smaller than the human auditory cortex (volumes of 10-20 mm³ and 2500 mm³, respectively), their auditory memory capacity is expected to be about 100 times smaller than that of humans, potentially reaching values as small as 100 items. This may allow us to challenge the rats' ability to retain auditory memories. Two rats were trained to discriminate between pairs of natural sounds, associating each sound with different reward location. To achieve life-long learning, a new pair of sounds with corresponding reward locations was introduced weekly. Our results suggest that the rats indeed learn the new association successfully. Our next stage is to test memory retention of previously-learned sounds.

Advisor: Prof. Israel Nelken

A Comparative Evaluation of Eye Movement Detection Algorithms

Jonathan Nir

Eye tracking (ET) is a widely used method in cognitive research, often relying on detection algorithms (detectors) to parse raw data to discrete eye movements (EMs). Detectors vary in the EM types they can detect and their overall performance. Our work introduces pEYES, an open-source Python package designed to streamline EM detection and enable robust, quantitative comparisons between detection algorithms.

We evaluated seven commonly used detectors by applying pEYES to a publicly available dataset comprising 20 recordings of free viewing color images, with expert human annotation that served as the ground truth (GT). Performance was evaluated based on label agreement (Cohen's Kappa) with the GT, temporal alignment with the GT (relative timing offset and deviation), and ability to discriminate fixation and saccade onsets and offsets (d').

Results revealed significant performance differences. Engbert's algorithm, employing an adaptive velocity threshold, consistently outperformed others on fixation onset and offset detection, approximating the precision of human annotators. It performed slightly worse for saccades, though still comparable to other top-performing algorithms. Conversely, algorithms utilizing spatial dispersion thresholds underperformed across most metrics.

Our work establishes Engbert's algorithm as the optimal detector for fixations and saccades during free viewing tasks. Furthermore, it demonstrates pEYES as a versatile tool for EM research, fostering quantitative evaluations of EM detectors. The package is freely available, and we welcome feedback and collaboration to improve its functionality further.

Advisor: Prof. Leon Deouell

Investigating the Role of Secondary Motor Cortex in Sensory Processing and Motor Preparation During Decision Making Under Uncertainty

Haneen Rajabi, Gabrielle Marmur, John Schwarcz, Robert Reiner and Eran Lottem

Understanding how the brain integrates sensory inputs to guide decision-making under uncertainty is a fundamental question in neuroscience. Emerging evidence suggests that the secondary motor cortex (M2) plays a critical role in processing task-relevant information. Using an auditory-guided change detection task, we investigated how M2 contributes to adaptive behavior in dynamic environments. Our findings suggest that M2 activity reflects both sensory-driven processes and motor preparation, supporting its dual role in integrating auditory cues with behavioral demands. These findings advance our understanding of the neural circuits underlying sensory-motor transformation and highlight the critical role of M2 in enabling flexible behavior in dynamic and uncertain environments.

Advisor: Dr. Eran Lottem

The neuronal engram of inflammation-associated sickness behavior and its interaction with local microglia.

Lior Naggan

Inflammation exerts profound effects on both the body and brain, resulting in significant disruptions to physiological, behavioral, and cognitive functions. Prior research has established that inflammation-induced sickness behavior shares an overlap with depressive and anxiety symptoms that emerge during exposure to infections, stress, and a range of neuropsychiatric conditions. These symptoms have been linked to the activation of microglia, the brain's resident immune cells, and their potential interactions with neuronal circuits. However, the precise neuronal populations driving sickness and depressive symptomatology, along with the nature of their interactions with microglia, remain poorly understood. This research aims to identify the specific neuronal ensembles encoding a peripheral inflammatory challenge and utilize chemogenetic tools to manipulate these neurons in discrete brain regions to elucidate their causal relationships with sickness behaviors. Systemic inflammation was induced by an intraperitoneal injection of 500 $\mu\text{g}/\text{kg}$ LPS (the main activator of the immune system during bacterial infection) to mice, which were sacrificed 3.5 hr post-injection. We later stained brain slices for the immediate early gene cFos, which serves as a proxy for neuronal activity, thus revealing the neuronal population active at the peak of the response to the LPS challenge. We found increased LPS-induced neuronal activation in the central amygdala and the dentate gyrus of the hippocampus. Next, we delivered the excitatory chemogenetic receptor hM3DGq only to LPS-engram neurons in the central amygdala via AAV viral injections and activated them later using CNO. Activation of LPS-engram neurons elicited changes in sickness-behaviors such as increased anxiety, and cognitive disturbances in mice compared to controls. On the last day of behavioral tests mice were sacrificed during the time window in which CNO activates chemogenetic channels (approximately 4 hr) and brains were stained for the microglial marker Iba1. Our initial analysis revealed that LPS-engram neurons activation increased microglia density in the central amygdala. Together, these results highlight the central amygdala as an important region in mediating inflammation-induced sickness behaviors, which also affects local microglial changes.

Advisors: Prof. Raz Yirmiya and Prof. Inbal Goshen

When Do We Hear?

Maysan Bader

The perceptual center (P-center) of a sound is defined as the specific moment in time at which a sound is perceived to have occurred. P-centers can be estimated experimentally by Alignment tasks (aligning target sound with a click) or Tapping tasks (tapping to a isochronous beat of target sound). Previous studies have shown that the p-center is affected by sound structure, proficiency in music, task, and many other factors. Here, we relate the P-center to the neural mechanisms subserving auditory perception. We estimated P-centers for a set of validated sounds, and simultaneously recorded their ERPs. I will present preliminary data showing that differences in P-centers of sounds may be reflected in the latency of the N1 component in ERPs evoked by these sounds. This may indicate that the variations in p-center are the result of variations in the time of the auditory processing.

Advisor: Prof. Israel Nelken and Prof. Leon Deouell

Astrocytic Cellular Memory link Past Experience to Responses to Alzheimer's Disease Risk Factors

OR

Astrocytic Memory of Past Exposures Shapes Cellular Responses and Alzheimer's Disease Risk

Nadav Elan Eliash, Anna Kristina Schmidner, Daniel Kitsberg, Naomi Habib

Alzheimer's disease (AD) initiation and progression is associated with multiple risk factors and stress signals, including DNA damaging agents, oxidative stress, and inflammation. Extensive studies indicate a strong effect of each stressor on brain cells and the risk for developing AD, yet despite the strong link between these risk factors and their expected accumulation with age, the effect of their combined sequential exposure on brain cells is largely unknown. In this study, we investigate how exposure to initial stressors modifies cellular responses to subsequent challenges, exploring the concept of cellular memory in the context of AD risk factors. In particular, we focus on astrocyte cells, recently shown to transition to a stress-associated state in human AD and implicated as potential drivers of cognitive decline.

We first screened the range of responses by exposing primary astrocytes to various AD-associated stress stimuli and early pathological hallmarks. These stimuli were designed to mimic key pathological events common in aging brains that could influence the progression of AD. Next, we examined how these stressors and stimuli might be encoded in cellular memory and impact the astrocytic response to a subsequent challenge, whether by the same or a different stimulus.

Using RNA sequencing, we have recorded cellular responses and performed differential gene expression analysis and gene co-expression network analysis to identify coordinated changes in gene programs and to isolate pretreatment effects. We uncovered a manifold spanning diverse astrocyte responses, reflecting the range of states observed in aging human brains. Notably, different stimuli seemed to be encoded to variable degrees in astrocytic memory, with the potential to either enhance or diminish subsequent responses to additional stimuli.

This study provides insights into how past exposures shape acute responses in astrocytes, potentially influencing the convergence to neurotoxic or neuroprotective states that affect AD progression. Understanding these adaptive mechanisms could open new avenues for astrocyte-targeted therapies in neurodegenerative diseases.

Advisor: Dr. Naomi Habib

Early Neuronal Reprogramming is Shaping the Alzheimer's Disease Cascade

Roi Meir, Gali Schwartz, Naomi Habib

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by synaptic dysfunction and neuronal loss that lead to cognitive decline and dementia. Recent large-scale efforts to map the cascade of cellular events leading to AD in human brains, revealed a coordinated response of all glial cells, emerging at early disease stages, and predicted to drive the progression of the disease. Yet despite the known damage to neurons in AD, these efforts did not uncover at which stage of the disease the alteration in neuronal cells occurs and to what extent are these driving the cascade of events leading to dementia.

Here, we applied a continuous modeling approach to capture cellular diversity in a large dataset of 1.7 million single nuclei RNA profiles from 437 aging and AD prefrontal cortex human samples. Instead of a traditional discrete classification approach based on clustering, we used Topic Modeling to model the continuous diversity of expression programs within each brain cell type. Using non-negative matrix factorization (NMF), the RNA profile of each cell is decomposed into multiple gene expression programs that together describe the activity of the cell. Next, we identify programs dynamically regulated along the cascades of disease and aging.

In neuronal cells, we uncovered a coordinated change in the expression programs across all neuronal subtypes along the AD trajectory. Interestingly, these neuronal changes occurred at an early disease stage, well before the reported neuronal damage and cognitive decline, suggesting neuronal reprogramming as an early driver event in the AD cascade. In AD, neurons down-regulated the expression of basic functions, including synaptic genes, suggesting early synaptic modulation or damage. Surprisingly, our results suggest that neuronal fate in AD included two distinct programs, one leading to oxidative-stress and apoptosis cell death, while the other leading to re-entry into the cell-cycle. These dramatic rewriting of neuronal cells is tightly linked to the previously observed changes in glial cells, including an early response in microglia and astrocytes and a later cross-glial stress response and loss of myelin production in oligodendrocytes accompanying a major loss of synaptic proteins.

Advisor: Dr. Naomi Habib

Cocaine Disrupts Activity In An Appetitive Sub-Population Of Insula Neurons

Tomer Sheinfeld

Cocaine is a highly addictive and extensively studied drug that primarily affects the brain through the dopaminergic system. While it is well known for its rewarding and addictive properties, chronic high-dose use is toxic and is also associated with reduced weight and appetite, along with aversive valence. In this study, we unveil a sub-population of anterior insula neurons that is strongly downregulated by both acute and chronic cocaine exposure. Our preliminary data suggest that this neuronal population mediates the aversive and potentially toxic properties of the drug.

Our previous research has identified the ventrolateral striatum (VLS) as a key brain region influenced by cocaine. The VLS integrates inputs from various brain regions, and it encodes mouth- and tongue-related behaviors. Notably, we have demonstrated that both acute and chronic cocaine exposure recruits direct pathway neurons in the VLS, facilitating cocaine-induced orofacial stereotypic behaviors (Gonzales, 2020; Gonzales & Shalom, in preparation). Here we sought out to investigate cocaine-induced plasticity in inputs to the VLS.

We decided to focus on insula projections to the VLS, following a rabies virus retrograde tracing experiment - which indicated synaptic plasticity at insula synapses onto indirect pathway striatal neurons (iSPNs). We recorded the activity of this insular sub-population using fiber photometry and neuropixels combined with antidromic optotagging. Our findings reveal a decrease in firing rates and correlations in these neurons following cocaine exposure. Furthermore, we demonstrate that the inhibition of this population carries aversive properties, potentially elucidating the previously unexplained phenomenon of 'cocaine-induced conditioned taste aversion.'

Advisor: Prof. Ami Citri

Late development of innate olfactory circuitry

Taha E, Shapira S, Nahari R, Yudco O, Givon M, Segev I, and Mizrahi A

Innate olfactory behaviors, such as attraction to food odors and avoidance from predator scents, are traditionally considered hardwired and functional at birth. However, the functional ontogeny of such behaviors and their underlying neural circuitry remain completely unknown. We show that odor attraction and avoidance behaviors emerge only late in postnatal development. Juvenile mice exhibited weak and inconsistent responses to attractive and aversive odors, while adults displayed robust preferences. Anatomical analyses revealed that mitral cell (MC) projections to the cortical amygdala (a known critical node for innate odor preference) are immature in juveniles. Tracing studies further revealed distinct anatomical and physiological biases between MCs projecting to the cortical amygdala versus those projecting to the piriform cortex.

Using two-photon calcium imaging and computational decoding of mitral cell population activity, we showed that juvenile MC ensembles exhibit inferior precision and reliability of odor representations as compared to adults. Adult MCs projecting to the cortical amygdala displayed robust and sustained responses to aversive odor, underscoring their specialized role in innate odor processing. Remarkably, using wireless optogenetics to activate MC projections to the cortical amygdala in juveniles, we restored innate odor preferences to adult-like levels. These findings challenge the notion of innateness-at-birth by revealing a gradual maturation process of olfactory circuits, highlighting their critical role in activating innate behaviors.

Advisor: Prof. Adi Mizrahi

Cross-Pollination @ ELSC: Integrating Cognitive and Systems Neuroscience to Study Autism Spectrum Disorder

Aviel Sulem, Benne Praegel, Jaroslav Slobodskoy-Plusnin, Adi Mizrahi, and Merav Ahissar

An overarching goal in our ELSC community is to join forces across disciplines to tackle some of the most challenging problems in neuroscience. Achieving this goal is inherently difficult, as it involves overcoming a range of obstacles—from differences in experimental design approaches to semi-cultural disparities across fields.

In this project, the Mizrahi and Ahissar labs joined forces to bridge this interdisciplinary gap, aiming to uncover the neural basis of cognitive biases in Autism Spectrum Disorder (ASD). Specifically, we started by proposing a novel mechanism for the atypical use of context in ASD, gaining insights by integrating mouse and human studies. To this end, we assembled an interdisciplinary team that combines systems neuroscience and cognitive neuroscience, enabling us to approach the problem from multiple perspectives.

We explored ASD through the lens of perceptual learning and behavioral biases. Using the 16p11.2 deletion mouse model of ASD, a well-characterized preclinical model, we compared behavioral performance in an auditory discrimination task between ASD mice and matched controls. This comparison revealed that ASD mice are particularly sensitive to reward – and tend to press following Hit responses. Namely, they tend to repeat responses that led to reward. This discovery sparked the idea of a human counterpart phenomenon, leading us to assess behaviorally and with EEG sensitivity to reward in humans. Here too we found enhanced sensitivity compared to neurotypicals.

Taken together, our work suggests a shared pathway underlying a cognitive effect in ASD. This collaboration not only yielded new insights and hypotheses but also drove innovative research directions that will contribute to a deeper mechanistic understanding of ASD. Further, our partnership exemplifies how cross-pollination between disciplines can break traditional boundaries, generating meaningful discoveries that push the field forward.

Advisors: Prof. Adi Mizrahi, and Prof. Merav Ahissar

Decoding the Neural Representation of Ensemble Averages in the Lateral Occipital Complex

Noam Khayat

Ensemble perception refers to the visual system's ability to extract summary statistics of groups of similar objects, mainly manifested as the efficient perceptual averaging. While this phenomenon has been extensively studied and characterized behaviorally, its underlying neural mechanisms remain largely unexplored. Using functional magnetic resonance imaging (fMRI) and Multi-Voxel Pattern Analysis (MVPA), we investigated how the neural representation of ensemble averaging—specifically for line orientations—is decoded across cortical regions. Our experimental paradigm was designed to identify regions that encode explicit ensemble average information, with participants instructed to actively perceive and report the average orientation in a two-alternative forced choice (2-AFC) task. While some studies have suggested that the Parahippocampal Place Area (PPA) may specialize in ensemble perception and others have proposed that the neural representation of ensemble percepts is formed by pooling signals across multiple levels of the visual processing stream, our findings reveal that the Lateral Occipital Complex (LOC) also encodes ensemble average information, as evidenced by significantly above-chance classification accuracies. This result is novel and surprising, as the LOC is traditionally associated with object recognition and perception, independent of low-level visual features. We demonstrate that, beyond its well-established role in recognizing individual objects, the LOC also processes information of groups of objects perceived as unified wholes.

Advisor: Prof. Shaul Hochstein

Noise as a precursor to movement in neural and behavioral signals

Barak Haim, Mati Joshua and Yuval Hart

Movement is a complex task of synchronizing muscular activity in space-time with internal and external constraints. While specific phases of motion present clear kinematic profiles together with corresponding changes in neural activity, it is unclear when and how the transition from one segment to another occurs. Noise is usually thought to be masking the signal. However, we propose that changes in noise are indicative of upcoming changes in the signal. A key hypothesis of our work is that movement changes - especially those related to decision-making, intention, or strategy shifts - present observable early warning signals (EWS). These signals are innate to critical transitions in dynamical systems and as such, we expect them to manifest in neural and behavioral signals. For example, when an attacker shifts from stillness to a sudden attack, EWS manifest in subtle changes in motor variability, correlation, or other properties of the kinematic signal. Identifying EWS in movement and neural activity, would allow for the segmentation of continuous motion into meaningful sub-units, each corresponding to a distinct cognitive or motor phase. Using an EWS based segmentation system would allow tracking of intention and decision-making process.

To detect EWS signals, we have developed a codebase for analyzing time-series signals using various statistical indicators, based upon the theory of multiple time scale dynamics. We applied this framework to analyze signals from precise measurements of eye movements in monkeys. Our indicators pointed to changes in autocorrelation decay time (as well as other indicators) during the reaction time, just prior to the saccade onset. Consequently, we detected subtle, previously unknown changes in eye positional drift. Surprisingly, these changes did not indicate a drift toward the target but instead represented something entirely different. The EWS we have detected in the eye movements are indicative of critical slowing down, a phenomena characteristic of bifurcations in a dynamical system such as "pitchfork".

Advisors: Dr. Yuval Hart & Prof. Mati Joshua

Neural correlates of rapid learning in the Orbitofrontal cortex

Mousa Karayanni

Few-shot, rapid learning, enables us to swiftly grasp new knowledge and skills with little guidance or reinforcement. Computational studies emphasize the importance of abstract representations and generalization to rapid learning. Previous studies have revealed both correlative and causal relationships between the Orbitofrontal cortex (OFC) and these essential features of rapid learning. To directly investigate OFC with rapid learning, we developed a multi-step behavioral task to assess learning strategies in freely-moving rats while recording neural activity using untethered Neuropixels probes. Rats exhibited 4 or more episodes of rapid learning within single sessions, with near-optimal performance after only 1-2 rewards. The rats employed hierarchical, model-based problem-solving strategies, leveraging their understanding of task structure to achieve rapid learning. Electrophysiological recordings from the OFC revealed heterogeneous yet robust responses around task-related events, generating predictive and decodable task-related representations. Importantly, rapid learning was accompanied by systematic changes in neural responses, which reflected shifts in OFC information content.

Advisors: Prof. Eli Nelken & Prof. Yonatan Loewenstein

Revealing CA1 Circuit Mechanisms with Voltage Imaging During Virtual Navigation

Rotem Kipper, Yaniv Melamed, Qixin Yang, Gal Shturm, Shulamit Baror Sebban

Hippocampal place cells are thought to form the foundation of a cognitive map of space. To better understand the mechanisms underlying place cell formation, we performed intracellular recordings from diverse hippocampal cell types, accessing both spiking outputs and subthreshold inputs of excitatory and inhibitory cells in the CA1 microcircuit. To overcome the limitations of conventional electrode-based techniques, we expressed the genetically encoded voltage indicator Archon1 in CA1 pyramidal cells (PCs) or dendrite-targeting somatostatin-positive (SST) interneurons. Using holographic targeted illumination and high-speed imaging, we recorded membrane potential dynamics from ensembles of cells during navigation in familiar and novel virtual environments.

As expected, a significant fraction of PCs exhibited spatial tuning, with place fields tiling the virtual track and clustering near the reward zone. SST interneurons displayed diverse activity patterns, including speed-tuned firing, uniform firing along the track, and spatially tuned firing. While spatially tuned PCs showed characteristic asymmetric depolarization ramps within their place fields, SST cells exhibited symmetric subthreshold signatures, suggesting distinct underlying plasticity mechanisms.

In novel environments, both cell populations underwent global remapping. Notably, SST interneurons showed an unexpected increase in global firing rates during the initial laps of the novel environment, challenging the conventional view that dendritic inhibition decreases during remapping. During repeated imaging in familiar environments across weeks, SST interneurons demonstrated remarkably stable firing and subthreshold properties, whereas PC activity was more variable. Nevertheless, most PCs maintained stable place fields despite this variability and displayed little representational drift.

These findings provide new insights into the activity and stability of key CA1 microcircuit components during spatial navigation and mark a step toward a mechanistic understanding of hippocampal place cell formation and persistence.

Advisor: Dr. Yoav Adam

Inhibition of TRPV1 by an antagonist in clinical trials is dependent on cholesterol binding

Tal Brandwine-Shemmer^a, Baruch Minke^{a,*}, Irena Levitan^{b,**}

TRP Vanilloid 1 (TRPV1) channel, one of the major members of the TRP family was discovered to play a critical role in pain sensation, particularly inflammatory pain, and is associated with hyperalgesia, an enhanced sensitivity to pain. A new study by Fan et al. "*Structural basis of TRPV1 inhibition by SAF312 and cholesterol*" sheds new light on the mechanistic structural basis of TRPV1 inhibition by SAF312 (Libvatrep), a TRPV1 antagonist, currently in phase II clinical trials. They discover that the binding site of SAF312 in TRPV1 is in close vicinity and partially overlaps with the binding site of cholesterol and that removal of cholesterol interferes with the ability of SAF312 to suppress TRPV1 current. Molecular dynamic simulations by Fan et al showed that cholesterol exhibited stable binding to the pocket when SAF312 was present. However, after SAF312 was removed, cholesterol showed higher flexibility, in consistence with our studies showing that bound cholesterol molecules were highly flexible within their sites, behaving differently than the more traditional "drug-like" ligand molecules. Similarly, increased mobility of SAF312 was shown in the absence of cholesterol, suggesting that cholesterol contributes to SAF312 binding, which inhibits pH activation of TRPV1 current. It is important to note that TRPV1 is known for its polymodal nature, showing activation in diverse ways via different domains of the protein, including heat, pH and vanilloid compounds, such as capsaicin. Our docking analysis revealed that cholesterol binds to TRPV1 in a pocket that also binds capsaicin (the hot ingredient of Chille pepper), a potent activator of TRPV1. We, furthermore, found that cholesterol competes with capsaicin leading to suppression of capsaicin activation of TRPV1. It is therefore interesting to examine in future studies the inhibitory effect of SAF312 on TRPV1 current that is activated via other modalities of TRPV1 such as heat. Moreover, since vanilloids (e.g. capsaicin) operate in vicinity to the TRPV1 pocket where cholesterol binds, we expect that the competition between capsaicin and cholesterol that we discovered, might reduce cholesterol ability to stabilize SAF312 binding to TRPV1.

Advisor: Prof. Baruch Minke

Fatigue-associated tRNA-Ala fragments contribute to synaptic plasticity and behavioral Parkinson's disease impairments

Tamara Zorbaz

Parkinson's disease (PD) patients suffer sex-dimorphic neurobehavioral and cognitive symptoms of yet unknown molecular origins that impair their quality-of-life years before and after diagnosis, especially in mutations-carrying and female PD patients. Here, we report that mammalian-conserved short C-rich 3'-end tRNA-alanine fragments (3'-tRFs-Ala) coordinate such behavioral PD impairments by interacting with the neuronal non-coding RNA MEG3-long variant at its 3'-terminal exon pre-miR-770 region. Intriguingly, blood 3'-tRFs-Ala levels in GBA+-carrying PD patients co-declined with the severity of autonomic dysregulation and fatigue contributing to the risk of depression. Furthermore, PD patients' substantia nigra revealed sex-related dysregulation of 3'-tRFs-Ala levels and altered neuronal interaction with the MEG3-long domain. Correspondingly, exposing cultured dopaminergic-differentiated human neuroblastoma cells to PD pathology-related oxidative stress shifted 3'-tRFs-Ala from nuclear to cytoplasmic pool, altering their control over proteins involved in nuclear splicing and cytoplasmic tRNA-aminoacylation. Inversely, antisense oligonucleotide 'sponging' of neuroblastoma 3'-tRFs-Ala declined necroptosis-related MEG3 short variant levels while upregulating the cytoplasmic levels of 3'tRFs-Ala mRNA targets reshaping neuroplasticity and immune responses. Our findings highlight 3'-tRFs-Ala as fine-tuners of neuroplasticity-mediated PD behavioral impairments affected by the fatigue-associated peripheral immune responses.

Advisor: Prof. Hermona Soreq

Reverse-Engineering Single Neuron Computation: Insights from Biophysical Models Solving d-Parity Problems

Noam Pnueli

Neurons are the computational building blocks of the brain, yet the precise mechanisms by which they perform complex computations remain unclear. Previous research has demonstrated that single cortical pyramidal neurons can solve non-linear tasks, such as the d-parity problem, using the DendMapping algorithm, an effective differential optimization method that trains biophysically realistic neuron models by learning synaptic weights and axonal rewiring patterns. However, how these neurons exploit their computational capabilities to achieve such tasks remains an open question. Building on this prior work, our study investigates how biophysically realistic neuron models solve the d-parity problem, including the well-known 2-parity (XOR). Using the functional and structural synaptic configurations learned through the DendMapping algorithm, we reverse-engineered the underlying computations to uncover the neuronal dynamics that enable these non-linear algebraic operations. Our analysis reveals how neurons leverage both spatial and temporal aspects of their computation to implement high-dimensional non-linear functions. Specifically, solutions learned by the DendMapping algorithm for the 2-parity and 4-parity problems exploit time to decompose the problem into smaller linear subproblems and utilize the apical tuft as an independent computational unit, with its distance from the soma supporting a timing mechanism. Higher-dimensional parity tasks further utilize more advanced spatial and temporal tactics. While our findings provide new insights into the computational strategies employed by individual neurons, they also underscore the complexity of these processes and the need for further exploration to fully understand the functional potential of single-neuron computation.

Advisor: Prof. Idan Segev

Establishing an Experimental Framework to Investigate the Claustrum's Role in Psychedelic Drug Action

Liel Kinkel

Psychedelic drugs hold promise for treating treatment-resistant depression, anxiety, and PTSD, yet their neural mechanisms remain poorly understood. The claustrum, a highly interconnected brain structure, is gaining recognition as a critical node in the neural circuits influenced by psychedelics. With its unique receptor profile and involvement in sensory integration, cognition, and consciousness, evidence indicates that psychedelics disrupt the claustrum's typical modulatory functions. Specifically, psychedelic-induced inhibition of the claustrum is associated with reduced connectivity to the default mode network and a decrease in cortical low-frequency oscillations.

We hypothesize that serotonin binding to 5-HT_{2A} receptors mediates this inhibition, reducing the claustrum's modulatory control over cortical activity. This mechanism may enhance cortical excitation, allowing suppressed sensory and cognitive signals to emerge, contributing to the reorganization of perception and cognition observed during psychedelic experiences.

To calibrate an experimental framework within which we could study this question, we employed behavioral assays and photometry in a chronic stress paradigm using C57BL/6 mice exposed to 21 days of corticosterone treatment. Behavioral paradigms included the Tail Suspension Test (TST), Head Twitch Response (HTR), and Social Preference Test (SPT), with additional exploration of psilocybin's effects and their inhibition by the 5-HT_{2A} antagonist M100. Photometry experiments measured calcium activity in claustral projections to the anterior cingulate cortex (ACC) under psilocybin influence.

This study provides an experimental framework for understanding the claustrum's role in the antidepressant effects of psychedelics, advancing our knowledge of the neural mechanisms underlying their therapeutic potential.

Advisor: Prof. Ami Citri

Pareto optimality reveals the computational goals of the human brain

Dan Hilman Amir

The human brain performs a wide range of computations to support complex behaviors, reflected in diverse activity and connectivity patterns. Among the myriad of complex functional connectomes, can one disentangle these into meaningful core computations? Here, we propose a principled framework for connecting the brain's functional organization to computations — Pareto optimality. Pareto optimality theorem posits that systems optimizing performance under multiple competing goals achieve this by balancing trade-offs within a low-dimensional space called the Pareto front. The Pareto front is spanned by archetypes that optimize each goal individually. Thus, Pareto optimality implies strong constraints on the architecture of systems performing under competing goals. We applied Pareto analysis to reveal the driving computations of the human brain's resting-state functional connectome (HCP dataset, N=1200). We found that resting-state functional connectomes lie on a low-dimensional triangle, consistent with the geometric constraints of the Pareto front. The three archetypes correspond to three core computational goals: 1) energetic efficiency 2) control and goal-directed processing 3) internal processing and memory. These goals are reflected in the archetypes' connectivity patterns, network topology and information flow measures, and behavioral and clinical associations. These core computational goals extend beyond resting-state, as the Pareto front provided an effective coordinate system for evaluating brain functionality. Dynamics on the Pareto front corresponded to task demands, correlated with task performance, and outperformed PCA dimensions in task prediction accuracy. Using two additional datasets (ADHD-200 and ADNI), we found differing characteristics of young adulthood and aging along the Pareto trade-off axes. On top of these dynamics, ADHD adolescents and Alzheimer's disease patients showed distinct locations compared to their age-matched neurotypical population. Finally, a minimalistic neural computation model demonstrated the fundamental nature of these computational trade-offs in information processing systems. Taken together, Pareto analysis indicated that the functional organization of the human brain at resting-state is shaped by trade-offs between three core computational goals. On a broader scale, Pareto optimality offers a novel, principled framework to link neural architectures to core computations across modalities, tasks, lifespan stages, clinical conditions, and populations.

Advisor: Dr. Yuval Hart

A bidirectional interaction of learning and perception

Chaviva Markind

Perception of ambiguous observations is shaped by our expectations, which themselves are formed based on our percepts of previous ambiguous observations. In a dynamic environment, sensory ambiguity could make it difficult to distinguish between random local fluctuations (stochasticity) and lasting changes with future impact (volatility). It is currently not known how sensory ambiguity influences the learning of these properties, and how this learning in turn influences perception. We conducted a sound-localization task and found that participants could track the expected directions of the sounds, however this ability declined as sensory ambiguity increased. Moreover, participants' reported percepts of new sensory inputs were biased toward their expectations in a manner that accounted appropriately for all three sources of uncertainty. By incorporating computational modeling and self-report questionnaires, we linked people's psychopathological traits to their experienced levels of sensory ambiguity and their individual tendencies to infer volatility and stochasticity.

Advisor: Professor Eran Eldar

Judge a neuron by its cover -How does a neuron's morphology affect its computational complexity?

Einav Hermelin

Neurons exhibit significant variability in their morphologies, both across different species and between different brain regions. The computational implications of these morphological differences are largely unknown, especially, their impact on the complexity of functions a neuron can implement. A recent study introduced the FCI (Functional Complexity Index), a novel deep learning based method for measuring the input output complexity of neurons. By applying this method to assess the complexity of cortical pyramidal neurons in humans and rats, the researchers identified several morphological parameters that correlate with neuronal complexity, most notably, the overall size of the dendritic tree and its branching patterns. To generalize these previous research findings to arbitrary morphologies, we designed a synthetic set of morphologies inspired by Rall's tree model, systematically varying morphological parameters such as length, area, radius, and bifurcation patterns. We have validated a correlation between the length of the neuron and its complexity (FCI) in general morphologies. Moreover, we have found a complex relationship between the radii, the bifurcation depth and the complexity (FCI) of the neuron. By analyzing the key morphological features contributing to greater neuronal complexity, we elucidate the relationship between structure and function in neurons. Furthermore, identifying the functional differences among various neuron types may illuminate their distinct computational roles within the brain.

Advisor: Prof. Idan Segev

Voltage imaging in freely moving mice using Fiberscope and targeted illumination

Renana Malka, Shulamit Baror Sebban, Tal Sommer, Ori Katz, and Yoav Adam

Recent progress in developing Genetically Encoded Voltage indicators (GEVIs) and high-speed microscopy now allows optical intracellular recordings from ensembles of neurons in awake-behaving animals. While this technology opens exciting new frontiers in neuroscience research, it is currently limited to head-restrained animals. Here we combined a multi-core optical fiber relay, a high-NA Gradient refractive index (GRIN) lens, and holographic targeted illumination using a spatial light modulator (SLM), to allow voltage imaging in freely moving mice. We validated this approach in mice expressing the GEVI Ace-mNeon2 in the CA1 region of the hippocampus. We first show that targeted illumination significantly increases the signal-to-noise ratio (SNR) and reduces photo-bleaching. Next, we demonstrate the recording of spiking and subthreshold activity at a high SNR from CA1 Pyramidal cells and interneurons during free exploration of a 2D environment at the temporal resolution of 500 Hz and a spatial resolution of $\sim 1\mu\text{m}$. This novel experimental system paves the way for detailed mechanistic studies of neuronal dynamics during complex behavioral tasks.

Advisor: Dr Yoav Adam

Optimal Coding Model of Event Structure in Episodic Memory

Isaac Ashkenazi

Experience is continuous and noisy, yet our long-term memory forms cohesive, meaningful discrete episodes. Previous studies show that event boundaries are highly agreed upon and profoundly affect memory and recall – boundaries alter memory encodings, promoting the learning of recurring event categories and conforming to the latent generative modes of the noisy signals. Despite their significance, a clear account of the computational principle that governs memory segmentation is lacking. A common theory of memory segmentation suggests that boundaries correlate with abrupt stimulus changes, termed prediction errors. However, local prediction error detection alone cannot account for boundaries measured in gradually changing stimuli with constant prediction errors.

Our work explores the information-theoretical principle of optimal compression as the driver of segmentation. Our model is based on the Minimum Description Length (MDL) principle, which optimizes the trade-off between accuracy and parsimony of compressed representations, maximizing relevant information. The events produced by our model capture previous behavioral findings of event boundaries having larger prediction errors on average while also explaining occurrences of large errors within events. Our model can also learn the underlying structure of a noisy signal generated by the Chinese restaurant process without prior knowledge, explaining behavioral findings where memories capture the latent structure of the environment.

Advisor: Dr. Yuval Hart

Approximating rats' learning progress using Markov Decision Processes

Reut Cohen

Markov Decision Processes (MDPs) provide a robust framework for modelling complex behavioural tasks. Here I apply this framework to a sound localization task in the RIFF, a large arena for studying rat behavior while simultaneously recording neural activity (Jankowski et al. 2023). In this task, rats have to access the center of the arena, and then hear a sound from one of six peripheral 'interaction areas' (IAs). They then have to access that IA and poke into a port in order to collect reward.

We constructed an MDP that divides the arena into 7 sectors (one central and six peripheral), defines actions like moving, waiting, or poking, and assigns transition probabilities based on the task structure. Rewards are assigned in order to minimize movement before reward collection.

To quantify learning progress, we hypothesize that early in training, rat behaviour resembles a random uniform policy, while over time, behaviour increasingly aligns with optimal policies. We use KL divergence to measure the distance between the observed behaviour and the uniform random policy ('complexity'. We then optimize value (expected reward) under constraints on the complexity. We adapted G-learning (Fox, Pakman, & Tishby, 2016) for generating the information-limited optimal policies. These policies interpolate between a task-agnostic "don't care" policy and an optimal policy, simulating the gradual refinement of the rat's behaviour.

This approach provides a scalable framework for analysing learning in behavioural tasks, capturing nuanced dynamics missed by traditional success-based metrics.

Advisor: Prof. Eli Nelken

The role of the Ankyrin Repeat Domain (ARD) in the activation process of TRPV1

Rita Gutorov, Rachel Zaguri, Ben Katz and Baruch Minke

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Transient receptor potential vanilloid 1 (TRPV1), a receptor/channel for capsaicin and noxious heat, has been one of the most compelling targets for analgesics. Recently Katz, Zaguri, and co-authors (Katz et al 2023) reported on a human mutation of TRPV1 (*TRPV1^{N331K}*) at the ARD, which led to a complete functional knockout for all activation modalities. Here we investigated the fundamental question of how the N331K mutation, which is located at the cytosolic N terminal, at the ankyrin repeats domain of the hTRPV1 channel (i.e. “far away” from the channel pore region), affects all modes of channel activation causing a complete loss-of-function. The new model of stepwise activation of the channel, in which all channel subunits are involved, generating a “wave” of excitation that propagates through the ARD (Kwon et al., 2021) may explain how a critical mutation at the ARD may cause a complete loss of function phenotype, but it requires understanding of how each monomeric subunit contributes to channel activity. To answer this question, we generated and express in HEK cells a concatemeric construct, in which four TRPV1 monomers are covalently connect to each other using whole-cell voltage clamp and Ca²⁺ imaging experiments. We revealed that one wild type (WT) subunit is sufficient for some concatemeric TRPV1 activation, while 4 WT subunits show normal activity. Strikingly, insertion of increased number of mutant subunit to a single concatemeric TRPV1 channel decreased the currents in response to capsaicin. Surprisingly, we found that mutation in the first concatemeric subunit resulted in loss of function of the TRPV1 channel, regardless the identity of the other subunits, suggesting that the concatemer is not symmetrical. The main difference between the first concatemeric subunit and the other subunits is that the N-terminus of the first subunit is not connected by a linker, while the other three subunits are connected by linker. This difference may suggest that the N331K mutation is a dominant mutation. However, experiments in which we co-express tagged WT monomers together with tagged mutant monomers that can randomly form channels containing both WT and mutant subunits showed a 50% reduction of the response to capsaicin, indicating that the N331K mutation is not a dominant negative mutation. Together, the detailed understanding of how the N331K mutation at the ARD affects TRPV1 gating mechanism seems to require solving the effect of the mutation at various channel subunits at the atomic level, using cryo-EM of the mutated channel. Nevertheless, we can conclude that the concatemeric channel does not accurately mimic the WT channel, and that we have no satisfactory explanation to the question of why a mutation in the first subunit virtually abolished channel activity. Importantly, the results suggest subunit cooperativity in the mechanism of channel activation, in line with the model of stepwise activation via a “wave of excitation propagating through the ARD.

Advisor: ??

The neural basis of temporal scaling in natural behavior using temperature

Shai Tishby

Biological and neural processes are heavily dependent on temperature for proper function and yet there are animals that have to operate accurately in varying temperatures in their natural habitat. Zebrafish rely on their hunting behavior in varying water temperatures (18°C to 33°C). It remains unclear whether hunting behavior and its underlying visual or motor processing are affected by temperature changes. We recorded larval zebrafish hunting behavior in three ecologically relevant temperature conditions (cold, intermediate, and hot; 22°, 27°, and 32°C respectively). Subsequently, we recorded neural activity and tail movements in response to prey-like stimuli using two-photon calcium imaging under these three temperature conditions in each fish. While hunting performance remained robust across the different thermal conditions, the entire behavior was temporally scaled with temperature. In agreement with the robust hunting performance, neural decoding performance did not differ with temperature. In line with the temporal scaling of the behavior, neural dynamics in the hot condition were faster, and slower in the cold condition. These faster and slower dynamics could account for the change in tail beat frequency, movement duration, and the resulting similar hunting events. Our results suggest that temperature in this ecological range of 10°C, modulates temporal aspects of information processing and behavior generation in larval zebrafish, without affecting performance or accuracy.

Advisor: Dr. Lilach Avitan

Continuous decision making in a closed-loop auditory navigation task

Shai Yellinek

A central goal in neuroscience is to understand the neural basis of perceptual decision-making behavior. Traditionally, this is studied through paradigms that focus on discrete behavioral events, like pressing a lever or licking a water spout, in response to isolated stimuli. In these paradigms, both stimuli and actions are sparse, with information flowing in one direction - from stimulus to action - without feedback from actions influencing subsequent stimuli. In contrast, natural behavior is inherently different; it is continuous and involves an ongoing cycle of perception-action loops, where animals not only respond to stimuli but also actively influence them in the process.

In this work, we present a novel task that engages mice in a continuous sensory-control task, allowing us to investigate the neural mechanisms behind naturalistic decision-making. Our closed-loop auditory-navigation task requires mice to search for a random target location in an open arena to receive water rewards. They rely on an auditory stimulus - a pure tone whose frequency continuously changes depending on the mouse's orientation relative to the target. Consequently, the stimuli that guide behavior are also continuously changed by it.

We begin by showing that mice learn to perform this challenging task by using sound cues to guide their movements and locate targets efficiently. We then introduce a series of manipulations to the stimulus structure within the environment, demonstrating that mice are capable of adaptive responding to a continuously changing input stream within dynamic closed-loop settings.

To investigate the role of cortical processing in this behavior, we pharmacologically inhibited the auditory cortex using focal application of the GABA-A receptor agonist muscimol. This inhibition produced a contralateral bias in sound sensitivity with minimal impact on overall locomotion. Based on these findings, we propose a computational framework involving cortico-striatal circuits to support continuous, sensory-driven control of locomotion.

Advisor: Dr. Eran Lottem

The Multifaceted Roles of WNT Signaling in Dorsal Neural Tube Development: The dynamic journey from Neural Crest to Roof Plate and subsequently to Dorsal Midline Radial Glia

Susanna Ventriglia

The development of the embryo is a remarkable demonstration of how time and space play a critical role in the formation of tissues and organs. A striking example to study these dynamics is the development of the dorsal neural tube. This highly dynamic process begins from the neural tube harboring neural crest (NC) progenitors that generate the peripheral nervous system. NC cells are precursors of sensory and sympathetic ganglia, Schwann cells and much more such as adrenomedullary cells and melanocytes. Next, this domain is replaced by the roof plate (RP), a patterning center for dorsal interneurons. Through a process of dorsal collapse, the RP gives rise to dorsal midline radial glial cells (dmRG) which eventually generate dorsal ependyma, a stem cell niche of the central nervous system. To investigate the spatio-temporal molecular repertoire and morphological changes that characterize the above transitions, we adopted a candidate approach by selecting genes from a recent single cell RNA-seq performed in our lab. A series of in-situ hybridizations were performed in quail embryos between embryonic days 4 to 13. Expression of BMP inhibitors present in RP, such as *Bambi*, *Raldh2*, *Hes4*, and *Grem1*, persist in the stretched RG. Likewise, components of the Wnt pathway such as *Axin2*, *Wnt1*, *Wnt3a* and its regulator *Rspo1* are present at both stages. In contrast, *Ism1*, *NANOS1*, *SLC1A3*, *Sox9*, *CXCR4*, and *Fabp7* are absent in RG, distinguishing the RP and RG stages and highlighting a distinct molecular profile exclusive to dorsal midline RG, which is absent in neighboring radial glial cells (you did not mention the genes present only in RG, so the previous sentence lack it full meaning, also divide the sentence into 2 shorter ones). By implementing the above genes, we are currently examining the functions of various morphogen signals, the dynamics of cell proliferation and the morphological changes in selected aspects of RP-to-RG transition. Along this line, we began exploring the role/s the Wnt pathway by implementing a loss of function approach, using time-dependent misexpression of a dominant negative *Lef1* (dNLef1) construct subsequent to the NC stage. In dNLef1-treated embryos, the development of RP traits was impaired, characterized by a cell autonomously RP-specific genes loss. This led subsequently to abnormal radial glia formation. This shows that Wnt activity is necessary both for RP and RG development. Experiments in progress will clarify the role/s of Wnt signaling at selected time windows spanning the period between NC to RP and RP to RG as well as investigating the role of other signaling pathways in the latter transition.

Supervisor: Professor Chaya Kalcheim

Implementing arbitrary nonlinear low-dimensional dynamical systems in large neural networks

Zhenyi Wang

A growing body of evidence underscores the importance of low-dimensional neural dynamics in motor systems, sensory pathways, and cognitive task representations. Prior attempts to link network structure to these low-dimensional activities have mainly employed low-rank perturbations of random synaptic weight matrices with Gaussian statistics, which significantly limit the networks' dynamic repertoire. To understand how neural circuits implement diverse computations, we need a theoretical framework that accommodates complex structures and arbitrary nonlinear low-dimensional dynamics.

We tackle this challenge by considering low-rank connectivity matrices with higher-order statistics. By deriving a dynamic mean-field theory, we capture the low-dimensional activity generated by such structured connectivity, elucidating the relationship between connectivity rank, dimensionality, and dynamical expressivity.

To demonstrate the power of our approach, we present concrete examples. First, we generate a low-dimensional attractor with multiple fixed points, mirroring representations found in the motor cortex during preparatory behavior, demonstrating that connectivity rank nontrivially influences representational dimensionality. Using low-rank connectivity, we construct combinations of fixed points, line attractors, and slow points, providing essential building blocks for various computations. Furthermore, we construct a low-dimensional chaotic attractor with high pairwise correlations, distinguishing it from the high-dimensional chaos of large random networks. Crucially, we demonstrate that the dynamics learned by low-rank structures remains robust despite noise and chaotic fluctuations induced by weight disorder. Finally, we prove the expressive power of rank for approximating arbitrary low-dimensional dynamical systems, particularly, demonstrating that these errors decrease exponentially with connectivity rank.

Our work bridges a critical gap between network structure and neural dynamics, offering a prescription for constructing neural networks capable of implementing nonlinear dynamical systems using low-rank structures and providing a robust framework for analyzing trained networks. This advancement opens new avenues for understanding and designing neural circuits that mirror the brain's complex computations.

Advisor: Prof. Jonathan Kadmon

A neural basis of adaptive decision-making in dynamic and uncertain environments

John Schwarcz

Cognitive flexibility—the ability to rapidly adapt to changing environments with uncertain and incomplete information—is crucial for survival. However, the mechanisms that allow updating belief states in dynamic environments without immediate rewards remain poorly understood. We address this challenge by developing a theoretical framework for sequential Bayesian belief-state updates, which we test using artificial neural networks and rodent behavioral experiments. We introduce a novel change-detection task designed to capture the complexities of decision-making in partially observable environments. Analysis of this task reveals a counter-intuitive feature of Bayesian decision-making: in environments with greater uncertainty, the decision variable is closer to the threshold, contrary to the expectation that it would be further away to allow for more evidence integration. This proximity is offset by slower integration, reflecting the input uncertainty. Neural networks trained with reinforcement learning exhibit this Bayesian signature in their dynamics and achieve near-optimal performance. Notably, behavioral analysis of the rodents reveals qualitative similarities with both the networks and the Bayesian model, suggesting that the brain may employ similar computational strategies for inference and adaptation. This distinct signature provides a testable prediction for future neuroscience experiments and highlights the unique role of Bayesian inference in cognitive flexibility and decision-making. By integrating theoretical models, neural network dynamics, and animal behavior, our work offers new insights into the neural mechanisms underlying adaptive decision-making in uncertain environments.

Advisors: Eran Lottem & Jonathan Kadmon

The Role of cerebellar output to the motor cortex in manual dexterity tasks

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Cerebellar output to the motor cortex plays a crucial role in the timing and coordination of multi-joint upper limb movements. Previous studies have described the specific contribution of cerebellar signals to the movements of proximal joints, whereas the control of distal joints (wrist and fingers) is considered to be under direct motor cortical control. Nevertheless, accumulating evidence suggests that the cerebellum may also be involved in controlling finger movements, although the way these signals control finger movements during manual dexterity tasks remains unclear.

We addressed this question by training a monkey to alternate between two motor tasks involving either proximal or distal joints for a food reward. Single cell activity was recorded from the primary motor and premotor cortices, contralateral to the working arm. The recording sites were identified using stimulation trains (333 Hz, 50 ms long) delivered through the recording electrodes. The cerebellar outflow was reversibly blocked using high-frequency stimulation (HFS, 130Hz) applied through a chronic stimulating electrode implanted in the superior cerebellar peduncle, ipsilaterally to the working arm. We used a video-based markerless tracking algorithm (DeepLabCut) to document movements of individual, proximal and distal joints and calculate the behavioral parameters during the control and HFS trials. The relationships between motor cortical activity and task performance were quantified by calculating the event-related modulation of firing rates.

We found that distal finger-related sites in the motor cortex were strongly driven by the cerebellar outflow, although to a lesser extent than proximal shoulder-related sites. Blockage of the cerebellar output by HFS led to a significant decrease in firing around the onset of the reaching movement in the proximal (23%) and distal (12%) sites. When the monkeys were engaged in the manual dexterity task, HFS led to altered joint kinematics accompanied by a drop in task-related activity. Taken together, these findings suggest that cerebellar signals drive finger-related motor cortical sites, since their absence leads to both reduced neural activity in these sites and impaired dexterous behavior. These results thus support previous reports of cerebellar involvement in controlling finger movements in non-human primates.

Advisor: Prof. Yifat Prut

Weighted MRI Ratios as Proxies for qMRI in Alzheimer's Disease

Shachar Moskovich

Weighted MRI images are widely used in clinical as well as open-source neuroimaging databases. Weighted images such as T1-weighted, T2-weighted, and proton density-weighted (T1w, T2w, and PDw, respectively) are used for evaluating the brain's macrostructure; however, their values cannot be used for microstructural analysis, since they lack physical meaning. Quantitative MRI (qMRI) relaxation rate parameters (e.g., R1 and R2), and related relaxivity coefficients, do contain microstructural physical meaning. Nevertheless, qMRI is rarely done in large-scale clinical databases.

Currently, the weighted images ratio T1w/T2w is used as a quantifier to approximate the brain's microstructure, and was previously shown to be linked with clinical Alzheimer's disease markers (Luo et al., 2019; Lim et al., 2023). Here, we propose three additional quantifiers that approximate quantitative maps, which can help bring quantitative MRI to the clinic for easy use.

Following the signal equations and using simple mathematical operations, we combine the T1w, T2w, and PDw images to estimate the R1 and R2.

We find that two of these quantifiers (T1w/PDw and T1w/ $\ln(T2w)$) can serve as a semi-quantitative proxy for R1, and that ($\ln(T2w/PDw)$) can approximate R2.

We apply these quantifiers on ADNI dataset in three brain regions that are known to be linked with Alzheimer's pathology: Hippocampus, Amygdala and Entorhinal cortex. We find that 3 out of the 4 quantifiers we examined show significant differences between clinical groups.

In summary, we propose a way to utilize weighted images, which are commonly used in clinical assessment of Alzheimer's disease, to approximate quantitative MRI parametrization.

Advisor: Prof. Aviv Mezer

Diverging and converging mechanisms in polyQ-related diseases

Shalhevet Klemfner

Polyglutamine (polyQ) diseases are a group of nine neurodegenerative disorders caused by the expansion of CAG trinucleotide repeats in specific genes, leading to toxic polyglutamine tracts in the encoded proteins. Although the genetic basis of these disorders is well-established, the molecular mechanisms driving selective neuronal vulnerability remain elusive. Emerging evidence highlights aging and epigenetic dysregulation as critical factors in polyQ disease progression.

Spinocerebellar ataxia types 3 (SCA3) and 6 (SCA6) are two polyQ diseases characterized by spinocerebellar ataxias. Despite their shared phenotype, SCA3 and SCA6 differ significantly in the functions and expression patterns of their affected proteins, ATXN3 and α 1ACT, respectively. These differences, coupled with their common pathological features, make them ideal models for comparative analysis.

This study investigates the normal and mutant functions of ATXN3 and α 1ACT using stem cells and brain organoids to model disease progression. By examining their roles in epigenetic regulation across developmental stages, from stem cells to mature neurons, we identify shared and disease-specific mechanisms underlying polyQ disorders.

The findings from this study could illuminate key molecular pathways driving neurodegeneration in polyQ diseases, offering potential targets for therapeutic interventions that address these debilitating conditions.

Advisor: Professor Eran Meshorer.